INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: HYDROPHILIC SIGNAL OLIGOPEPTIDES AND METHODS OF THERAPEUTIC USE

(57) Abstract

The instant invention is directed to a method of identifying signal oligopeptides through the use of algorithms, the use of signal oligopeptides as vaccines and as immunogens to produce antibodies.

HYDROPHILIC SIGNAL OLIGOPEPTIDES AND METHODS OF THERAPEUTIC USE

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Field of Invention

This patent is a continuation in part patent to serial number 07/997,727 and 08/045,394 which introduced new oligopeptide sequences based on the discovery of the protein code. The present patent claims further specific signal oligopeptides, further specifications of the methods of their identification, their therapeutic use as well as their application for diagnostic purposes.

References

1. Watson JD, Crick FHC. 1953. Nature 171: 737
2. Rath, M. 1993. J. Orthom. Medicine 8: 11
3. Rath, M. 1994. J Appl. Nutr. (in Press)

Background

This patent summarizes the discovery of the protein code and claims the therapeutic and diagnostic use of this new biological language for different areas of medicine.

The discovery of the genetic code four decades ago defined the principles by which genes encode for proteins (1). The protein code, however, the biological language by which proteins act and interact has remained obscure. Now the protein code is discovered (2,3). The interaction of hormones and other ligands with their respective receptors, of enzymes with protein substrates, of adhesive proteins with integrins, and of antibodies with antigens as well as other protein actions and interactions are determined by the same structure/function principles and the same biological language. For a very limited number of proteins the hydrophobic interior of the protein forms the active center which also determines their function. In the vast majority of proteins, however, biological activity is primarily mediated via specific surface structures which mediate their specific functions. The structure/function principles determining these protein actions are discovered (1) and they are hereafter referred to as the protein code

Summary of the Invention

Like the human language the protein code consists of letters words and sentences The letters (amino acids) and sentences (complete three dimensional protein) had been known before. The new discovery are the protein words or verbs. These protein verbs are represented by signal oligopeptides which are localized on the surface of the protein and are represented by the hydrophylicity maxima of the protein. These signal oligopeptides are enriched in charged amino acids in a versatile arrangement with neutral spacer amino acids The specific signal character of these oligopeptides is determined by a characteristic combination of conformation and charge within the same signal sequence

Like in the human language the whole sentence (complete three dimensional protein is needed

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to determine the specific and complete action of any given protein. In the human language eliminating or changing the verb of a sentence renders the whole sentence meaningless. Similarly, blocking the protein code verbs (signal oligopeptides) can be therapeutically used to block the undesired action or interaction of an entire protein.

The discovery of the protein code provides the rationale for deciphering the communication code of diseases. Infectious diseases, cancer, cardiovascular and other diseases develop by means of one or more pathogenicity-mediating proteins. Blocking the signal oligopeptides of these proteins allows the specific therapeutic interception of a pathological communication and thereby blocks disease propagation.

Synthetic analogs to signal oligopeptides can be used therapeutically in several ways. First, synthetic analogues to signal oligopeptides can be used as competitive inhibitors of pathological communication. Second, synthetic analogs to signal oligopeptides can be used as vaccines. This second therapeutic approach makes use of the fact that signal oligopeptides on the surface of the protein are identical with the antigenicity determining epitopes of this protein. Thus, antibodies are interceptors of metabolic communication. By binding to the signal oligopeptide of a protein antibodies and other mediators of immune response reduce or block its metabolic interaction. If synthetic analogs to signal oligopeptides are used as vaccines it is necessary to render these peptides antigenic and to allow their discrimination as 'non-self'. Synthetic analogs to signal oligopeptides can be rendered immunogenic by coupling them to haptens and by other conventional methods.

This patent also claims new methods by which oligopeptide sequences can be rendered immunogenic. This new method is based on the discovery of the primary structural principles determining immunogenicity. The discrimination between self and non-self between species and between individuals is primarily based on amino acid residue substitutions or other residue variations within the signal oligopeptide sequences of a protein. By making use of this discovery effective therapeutic signal oligopeptides can be rapidly produced in the following way: signal oligopeptides of a given protein in one species are the antigenicity determinants of this protein in another species. To block the action of a pathogenicity-mediating protein in the treatment of a human disease the synthetic signal oligopeptide vaccines are designed by copying corresponding amino acid signal sequences from another species. A glucagon signal oligopeptide vaccine for the treatment of diabetic patients would be based on glucagon signal sequences from rabbits, sheep, mice or other species. A titration of the therapeutic efficiency is possible: The greater the genetic and evolutionary distance of the selected species to humans the greater its antigenicity and, consequently, the greater its therapeutic efficiency as a vaccine.

This patent also includes claims for the use of new algorithms to identify signal oligopeptides. Moreover, claims are made to use the technology presented in this patent for the development of specific antibodies with predefined specificity and characteristics and their *in vitro* use for diagnostic purposes

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Detailed Description of the Figures

Figure 1. This figure illustrates several of the protein code principles. *Legibility:* Within the amino acid sequence of a protein one or more oligopeptides represent the words - or verbs - of the protein code which mediates its action and interaction. *Accessibility:* The signal sequences of a protein are enriched in charged amino acids and represent the hydrophylicity maxima within the potential sequence (Figure 1A). *Variability:* An infinite number of possible combinations between amino acids with different charges as well as neutral residues provide the variability for differentiated metabolic communication. *Specificity:* The specificity of a signal sequence is the result of a characteristic combination of charge distribution and structural conformation within the signal oligopeptide sequence. Oppositely charged amino acids can attract each other thereby enhancing confirmational specificity. Signal oligopeptides mediate specific information transfer to their metabolic counterparts (Figure 1B). *Differentiation:* Substitution, deletion or other amino acid residue variations within the signal sequence of a protein enable differentiation between 'self' and 'non-self'. Signal sequences are the antigenic epitopes of a protein and are responsible for potential immune responses when exposed to other organisms. *Interception:* Direct and indirect Peptide Interception Therapy (PIT) can be used to intercept undesired or pathological communication and thereby block the disease. In direct PIT synthetic analogs to signal oligopeptides can be used to competitively inhibit the interaction of proteins (Figure 1C). Indirect PIT makes use of synthetic oligopeptides rendered immunogenic These vaccines stimulating the production of antibodies which block pathological communication pathways not only in the prevention and treatment of infectious diseases but also in the therapy of neoplastic diseases, metabolic disorders and other diseases (Figure 1D).

Figure 2. Fundamentals of Peptide Interception Therapy (PIT). Proteins are essential carriers of specific metabolic information; moreover, proteins are frequently mobile which makes them ideal and versatile communication molecules. This figure illustrates several key elements of PIT: PIT is an interception therapy. To *promote protein action*, the entire three dimensional protein structure (protein sentence) is required. To *intercept protein action*, only the signal oligopeptide (verb) has to be blocked by direct or indirect PIT

Figure 2 shows the principles of Direct Peptide Interception Therapy (Direct PIT) including the methods for identification, design, development and therapeutic use of synthetic analogs to signal oligopeptides in Peptide Interception Therapy as direct competitive inhibitors of selected protein actions.

Figure 3. This figure shows the principles of Indirect Peptide Interception Therapy (Indirect PIT) including the methods for identification, design, development and therapeutic use of synthetic analogs to signal oligopeptides in Peptide Interception Therapy as vaccines to stimulate a specific immune response with the aim to decrease or block selected protein actions.

Figure 4. This figure shows the principles of Peptide Regulation Therapy (PRT) including the methods for identification, design, development and therapeutic use of synthetic analogs to signal oligopeptides in Peptide Regulation Therapy as negative feed-back regulators for the synthesis rate of selected proteins

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Figure 5. Amino acid sequence selection and therapeutic design of peptide vaccines for Indirect Peptide Interception Therapy, exemplified for the development of glucagon vaccines in clinical therapy of diabetes mellitus.

Figure 6. Peptide therapy in diabetes. This figure shows the potential signal sequences of proglucagon and therapeutic alternatives for peptide therapy in diabetic patients. Conventional treatment in diabetes focuses on an increased availability of insulin. Peptide therapy enables an alternative approach. Synthetic analogs to the signal sequences of glucagon can be therapeutically used to attenuate the effect of this insulin antagonist. Note the three hydrophilicity peaks in the glucagon precursor sequence (A,B,C). The mature glucagon hormone is activated by contact and charge redistribution within the peaks A and C. PIT therapy could have two distinct targets: Blocking charge redistribution of precursor molecule (PIT for Peak A or C) prevents activation of precursor to mature hormone. PIT targeting peak B prevents the action of the glucagon hormone. Vaccination with synthetic glucagon signal oligopeptides rendered immunogenic could become a baseline treatment for diabetic patients.

Figure 7. Peptide therapy in HIV infections. Synthetic analogs to signal oligopeptides of the HIV envelope protein GP 160 or the cell receptor CD4 can be used as vaccines. The specific antibodies produced should effectively inhibit the infection of cells. The hydrophylicity blot revealing potential signal sequences of GP 160 is shown in the upper part of the figure. Other targets of HIV peptide therapy are the regulator proteins Rev and Tat with the aim to block viral replication.

Detailed Description of the Invention

Decisive inventions have been presented in my earlier patent s with the serial numbers 07/997,727 and 08/045,394 This continuation in part patent includes further details and a comprehensive understanding of the principles of the Protein Code as well as of Peptide Interception Therapy (PIT) They are summarized as follows:

I.   Determining Principles of the Protein Code

The protein code is determined by the following principles:

1. *Universality.* The protein code is universally valid Proteins are important carriers of metabolic information in living organisms. The protein code is the biological language for protein-mediated information transfer during health and disease. The protein code is the underlying communication principle for the interaction of antigens with antibodies, enzymes with substrates, receptors with ligands, adhesion molecules with integrins and other forms of protein communication

2. *Compatibility.* The protein code is compatible with other elements of biological

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communication. The protein code and the genetic code are closely connected. The genetic code determines the structure of proteins and, thereby, their function. The protein code determines the relation between structure and function within a protein sequence and, thereby, the specific biological action. Specific and efficient action of a protein are responsible for the advantage of a gene and, therefore, for the survival of the genetic information encoding for the protein.

3. *Legibility*. The protein code is composed of letters, sentences and words. The protein code *letters* are represented by the amino acid residues of a protein. The protein code *sentence* is represented by the complete three dimensional structure of the protein which ultimately determines its action. The decisive signal of protein communication is mediated by the protein code *words*. These protein code words are represented by one or more signal oligopeptides within a protein sequence. In the human language verbs are the action words within a sentence. Signal oligopeptides are the verbs of the protein code and determine the action of the protein. Interference with these signal oligopeptides can lead to substantial modification or loss of the biological message of a protein.

4. *Accessibility*. The protein code has to be accessible. Protein information transfer and protein interaction is dependent on the accessibility of the signal sequence. Signal oligopeptides are generally represented by the regions of maximum hydrophilicity on the surface of the protein molecule. Critical determinants for these hydrophilicity maxima is an enrichment of the cationic amino acid residues arginine and lysine and/or the anionic amino acid residues glutamate and aspartate.

5. *Variability*. The protein code requires a sufficient reservoir of structural variations encoding for a large number of diverse signals. The protein code is based on optimum variability. The protein code is based on an almost infinite number of possible signal oligopeptide structures. A specific arrangement of charged amino acid residues in combination with a variable number of uncharged residues within signal tripeptides, tetrapeptides, pentapeptides, hexapetides or larger polypeptides provide the necessary number of possible residue combinations for a giant signal reservoir.

A new type of signals is represented by oligopeptides which obtain their characteristic conformation by a specific arrangement of oppositely charged amino acid residues within this oligopeptide sequence These residues with opposite charge can attract each other thereby modulating a characteristic folding of this signal sequence. In the signal sequence RGD the cationic residue arginine and the anionic residue aspartate attract each other leading to a characteristic folding of this tripeptide around the 'spacer' residue glycine.

6. *Specificity*. The protein code is specific. The specific and reliable metabolic function of a protein is dependent on the specificity of its biological signal sequences The signal character of a specific oligopeptide is determined by a characteristic combination of electrical charge with structural conformation. Within a protein, RGD and analogous tripeptides can serve as strong primary anchors while the specific biological message is mediated by additional longer and more complex signal oligopeptides.

7. *Differentiation*. The protein code provides the basis for the immunological differentiation

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between individuals and species. Substitutions, omissions, and other variations of one or more amino acid residues within the signal sequence of the protein enable an organism to differentiate between 'self' and 'non-self'. Thus, the protein code comprises the basic language of immunology.

8. **Diversification.** The protein code is a key for individual development within a species as well as for the evolutionary diversification of species. The effectiveness of signal oligopeptides to mediate specific biological messages were the ultimate criterion for the evolutionary advantage of a protein and, thus, for the evolutionary survival of the gene encoding for it. Genetic mutations leading to the substitution of one or more amino acid residues within a signal oligopeptide sequence were an economic and therefore frequent mechanism to modulate and differentiate protein action and thereby promoting evolutionary diversification.

9. **Interception.** The protein code is interceptable. The signal oligopeptides of a protein are identical with the potential antigenic determinants. Antibodies and other mediators of immune response are interceptors of specific biological communication. Signal oligopeptides as promoters of differentiated protein communication and immune response mediators as interceptors can form a sophisticated network of biological communication. Decoding the physiologic aspects of this communication network will lead to a precise understanding of millions of metabolic interactions including the principles for development and differentiation of the body. Decoding the pathophysiological aspects of this communication network will lead to the therapeutic control of many diseases and eventually to their eradication as causes of human mortality.

10. **Regulation.** The protein code could also provide a missing link in the regulation of protein synthesis. The signal sequences of a protein may have important feed-back functions directly or indirectly modulating the synthesis rate of this protein.

II. **Principles of Peptide Interception Therapy (PIT) and of Peptide Regulation Therapy (PRT)**

1. The metabolic interaction of proteins is primarily modulated by one or more oligopeptide signal sequences which determine the metabolic interaction of this protein. Peptide Interception Therapy (PIT) is defined as the specific therapeutic interception of pathological or undesired protein actions and interactions by the therapeutic use of synthetic analogs to the signal oligopeptide sequences of this protein. Peptide Regulation Therapy (PRT) makes therapeutic use of synthetic analogs to signal oligopeptide sequences to decrease the synthesis rate of an undesired protein via feed-back mechanisms.

· 2. Peptide Interception Therapy uses the discovery of the protein code: To *promote* protein action, the entire three dimensional protein structure (protein sentence) is required. To *intercept* protein

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action, only the signal oligopeptide (protein verb) has to be therapeutically blocked.

3. These signal oligopeptide sequences are located on the surface of the protein and are represented by the hydrophilicity maxima within the amino acid sequence of the protein. The signal oligopeptide sequences of a protein can be identified from its primary structure by use of a protein data base in combination with a suitable algorithm, such as for hydrophilicity or surface probability. In this algorithm the highest hydrophilicity or probability values have to be assigned to the charged amino acids lysine, arginine, aspartate and glutamate followed by asparagine and glutamine.

4. Synthetic analogs to signal oligopeptide sequences can be therapeutically used. An unlimited number of signal oligopeptide analogs can be synthesized covering the entire sequence of a selected hydrophylicity peak or parts of it.

5. Signal tetrapeptides, pentapeptides, hexapeptides and longer peptides represent primary candidates for specific peptide therapy. Shorter peptides, such as the tripeptide RGD, are less specific and ubiquitous side effects limit their broad therapeutic use.

6. Peptide Interception Therapy (PIT) can be used in two principal ways: Direct PIT uses synthetic analogs to signal oligopeptides as competitive inhibitors of pathological or undesired metabolic interaction. Indirect PIT uses these synthetic analogs as vaccines to stimulate the production of specific antibodies. In indirect PIT the antibodies, not the therapeutic peptide itself, function as interceptors of protein communication.

7. Direct Peptide Interception Therapy (Direct PIT) uses synthetic analogs to signal oligopeptides as direct competitive inhibitors for undesired protein communication. Direct blocking of pathogenicity mediating protein communication leads to the control of the related disease or clinical condition This therapeutic approach would be preferentially used in acute conditions, e.g. antithrombotic or fibrinolytic therapy. Direct PIT would be preferentially used intravenously in higher therapeutic dosages of the synthetic peptide Poly-oligopeptide analogs, time release delivery systems and other modifications of the peptide delivery mechanism can be used to extend the range of possible therapeutic applications.

8. Indirect Peptide Interception Therapy (Indirect PIT). Today vaccines are essentially limited to prophylaxis and therapy of infectious diseases. Indirect PIT enables the extension of the preventive and therapeutic use of vaccines to all areas of medicine. The great advantage of oligopeptide vaccines, compared to conventional vaccines, is that not the entire protein is used as a vaccine but only synthetic analogs to one or more of the signal oligopeptides of the selected protein.

9. Indirect PIT is based on the therapeutic use of antibodies produced by the patient's own immune system against the signal sequences of proteins mediating pathogenicity for undesired metabolic action. Indirect PIT is preferentially used for preventive therapy, for the treatment of chronic conditions or as adjuncts to direct PIT or other forms of acute therapy.

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10. Indirect PIT makes use of two newly discovered principles of immunology: First, the signal oligopeptides of a given protein are identical with its potential antigenicity determining regions (antigenic epitopes) Second, the primary mechanism determining antigenicity between different individuals and different species are amino acid residue substitutions, omissions and other residue variations *within* the signal oligopeptide sequence(s) of a protein.

11. Therapeutic peptide design for indirect PIT is based on the following principle: Signal oligopeptides of a given protein in one species are the antigenic epitopes of this protein for the immune system of another species. To block the action of a pathogenicity-mediating protein in the treatment of a *human* disease, the amino acid residue sequence of the oligopeptide vaccines should be homologous to the signal sequences of the same protein - but from *another species*. A glucagon signal oligopeptide vaccine for the treatment of diabetic patients would be based on the glucagon signal sequences from rabbits, sheep, mice or other species. The aim of this residue manipulation is to create an antigenic epitope without compromising the ability of the antibodies produced to effectively block the metabolic interaction of the protein. This therapeutic approach mimics nature's way to discriminate between 'self' and 'non-self' and make therapeutic use of it.

12. The designer of therapeutic compounds for indirect PIT can also make use of the evolutionary clock. The further apart two species are in evolution, the more amino acid residue mutations occurred, including mutations in the signal oligopeptide sequences, and the more antigenic is the therapeutic peptide composed of this sequence. A titration of the therapeutic efficiency of indirect PIT is possible: Indirect PIT therapy with synthetic analogs to glucagon signal oligopeptides from a *fish* species are more effective than those from a *mammalian* species in blocking *human* glucagon action.

13. Antigenicity required for effective indirect PIT therapy can also be stimulated in conventional ways, e.g. by coupling the therapeutic peptides to defined haptens or other immunogenic compounds enhancing 'non-self' recognition

14. A third therapeutic mechanism using synthetic analogs to signal oligopeptides is as feed-back regulators for protein synthesis. This form of therapy is designated Peptide Regulation Therapy (PRT). The synthesis rate of many proteins is determined by the amount of protein end-product available. The signal sequences of pathogenicity mediating proteins can be used to decrease the synthesis of this protein via direct or indirect feed-back mechanisms.

III. Use of Signal Oligopeptides for Development of *In vitro* Diagnostics

This patent also covers claims to use the technology presented for the production of in vitro antibodies for diagnostic purposes. In the future polyclonal or monoclonal antibodies for a protein can be manufactured in the following way

1. Identification of antigen. Synthetic analogs to one or more signal sequences of a

proteins are used as antigens. These signal sequences are determined from a data base by making use of algorithms for hydrophylicity or surface probability. For clinical diagnostics the signal sequence of the protein should preferentially be chosen from a database of human proteins.

    2. Optimum length of oligopeptide antigen. To optimize specificity of the antigen the signal oligopeptide should be at least a tetrapeptide or preferentially longer oligopeptides.

    3. Production of antigen. Polyclonal or monoclonal antibodies are raised according to established methods using adjuvants or other haptens.

    4. Testing of antibody specificity. The same synthetic signal oligopeptides used as antigens can be used to test the specificity of the antibodies.

IV. Advantages of Peptide Therapy

    1. Efficacy. Peptide therapy is a highly effective form of treatment. The discovery of the peptide code provides the rationale for deciphering the communication code of human diseases and allows the interception of pathological interactions with maximum effectiveness.

    2. Specificity. Peptide therapy enables maximum therapeutic specificity. Based on the precise understanding of the structure/function relation of specific protein signals, peptide therapy allows therapeutic targeting with unprecedented specificity.

    3. Safety. Peptide therapy is extremely safe. The use of synthetic analogs to physiologic compounds essentially eliminates the problem of toxicity. Possible undesired biological side-effects should be controllable by optimizing the length and composition of the therapeutic peptide

    4. Savings in therapeutic research and development. Time and expenses for the development of therapeutic peptides is a fraction of conventional therapeutic research and development Identification of potential therapeutic peptides takes minutes; in vitro screening of potential peptides is a matter of weeks; animal studies should provide first in vivo results within a few months. Most importantly, the unprecedented specificity and safety background of peptide therapy will allow clinical studies without delay.

    5. Advantage of peptide therapy compared to conventional therapies. The advantages of peptide therapy become even more obvious when this novel therapeutic approach is compared to conventional therapies or alternative future therapies *Conventional drug therapy* is frequently compromised by an unknown therapeutic mechanism and by a wide range of side effects and considerable toxicity *Gene therapy* is compromised by limited availability, its technological requirements and its high costs, which restricts its therapeutic application to exclusive areas in the foreseeable future.

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Heterologous or synthetic antibody therapy, the therapeutic application of antibodies produced outside of the patient's body, can cause incalculable adverse reactions by the patient's immune system against these 'foreign' antibodies. In contrast, peptide therapy makes elegant use of the patient's own immune system thereby excluding adverse immunological reactions.

V. Therapeutic Applications of Peptide Therapy

1. Infectious diseases. The most immediate application of peptide therapy is the prevention and treatment of infectious diseases. Every stage of any type of infectious disease is controlled by proteins which mediate adhesion, invasion and other mechanisms of pathogenicity. Effective therapeutic interception of biological signals within these pathogenicity-mediating proteins must lead to the control of the infection itself. Table I lists some of the most frequent infectious diseases and potential target proteins for peptide therapy. As discussed above, therapeutic peptides can be applied in acute treatment of infectious diseases and as vaccines.

2. Neoplastic Diseases. Another area with immediate applications for peptide therapy is the treatment of neoplastic diseases. Invasive growth and metastatic spread of any type of cancer is mediated by certain proteins and their signal sequences. Synthetic analogs to the signal sequences of these proteins should be developed as an effective therapy for different forms of cancer in their early stage as well as their invasive and metastatic stages.

3. Metabolic disorders. A novel therapeutic area for peptide therapy is the treatment of metabolic disorders. The potential of peptide therapy is exemplified here for the treatment of diabetes and hypertension.

Diabetes Conventional diabetic therapy aims at an increased availability of insulin Peptide therapy allows a novel and alternative approach by inhibiting the action of glucagon, the insulin antagonist. The inhibition of glucagon can be accomplished by using the therapeutic peptides analogous to the glucagon signal sequence for direct competitive inhibition or as a vaccine (Figure 5).

Hypertension. The renin angiotensin system and particularly the angiotensin-converting enzyme (ACE) are a continuous focus of antihypertensive drug development. Renin, angiotensin I and II as well as ACE are also promising targets for peptide therapy. Therapeutic use of synthetic analogs to the signal sequences of any of these proteins will lead to decreased blood pressure. Since in most cases hypertension is a chronic condition the therapeutic use of renin, angiotensin or ACE signal peptide vaccines should be considered.

Signal Sequences from the following proteins as well as their use for diagnostic and therapeutic purposes are claimed in this patent:

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Figure 1

A

B

C

Synthetic Analogs of
Signal Peptides
Competitively Inhibit
Interaction

D

Antibodies Against
Signal Peptides
Block Interaction

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<u>Figure 2</u>:   Direct Peptide Interception Therapy (Direct PIT)

Methods For Identification, Design, Development and Therapeutic Use of Synthetic
Analogs to Signal Oligopeptides in Peptide Interception Therapy
as Competitive Inhibitors Decreasing or Blocking Selected Protein Action

Selection of Protein in Computer Database

Identification of Hydrophylicity Maxima by Using
• Hydrophylicity Algorithm
• Surface Probability Algorithm
• Any Algorithm in Which Values Are Assigned
  to Amino Acid Residues in the Following Way:
  Charged Amino Acids > Uncharged Polar Amino Acids
  > Nonpolar Amino Acids
• Any Combination of the Above

Identify Signal Oligopeptides by
Selecting Hydrophylicity Maxima of Protein

Synthesize Synthetic Analogs to Signal Oligopeptides
(Therapeutic Peptides)

In Vitro and In Vivo Testing of Therapeutic Peptides as Specific
Competitive Inhibitors for Selected Protein Action

Test Positive

Test Negative

Clinical Testing of
Therapeutic Peptides

Optimization of Therapeutic Peptide
Size or Sequence by Amino Acid
Residue Substitution, Deletion,
Insertion etc.

Clinical Use of Direct PIT
Preferentially for, but Not Limited to
• Acute Therapy
• High Therapeutic Dosages
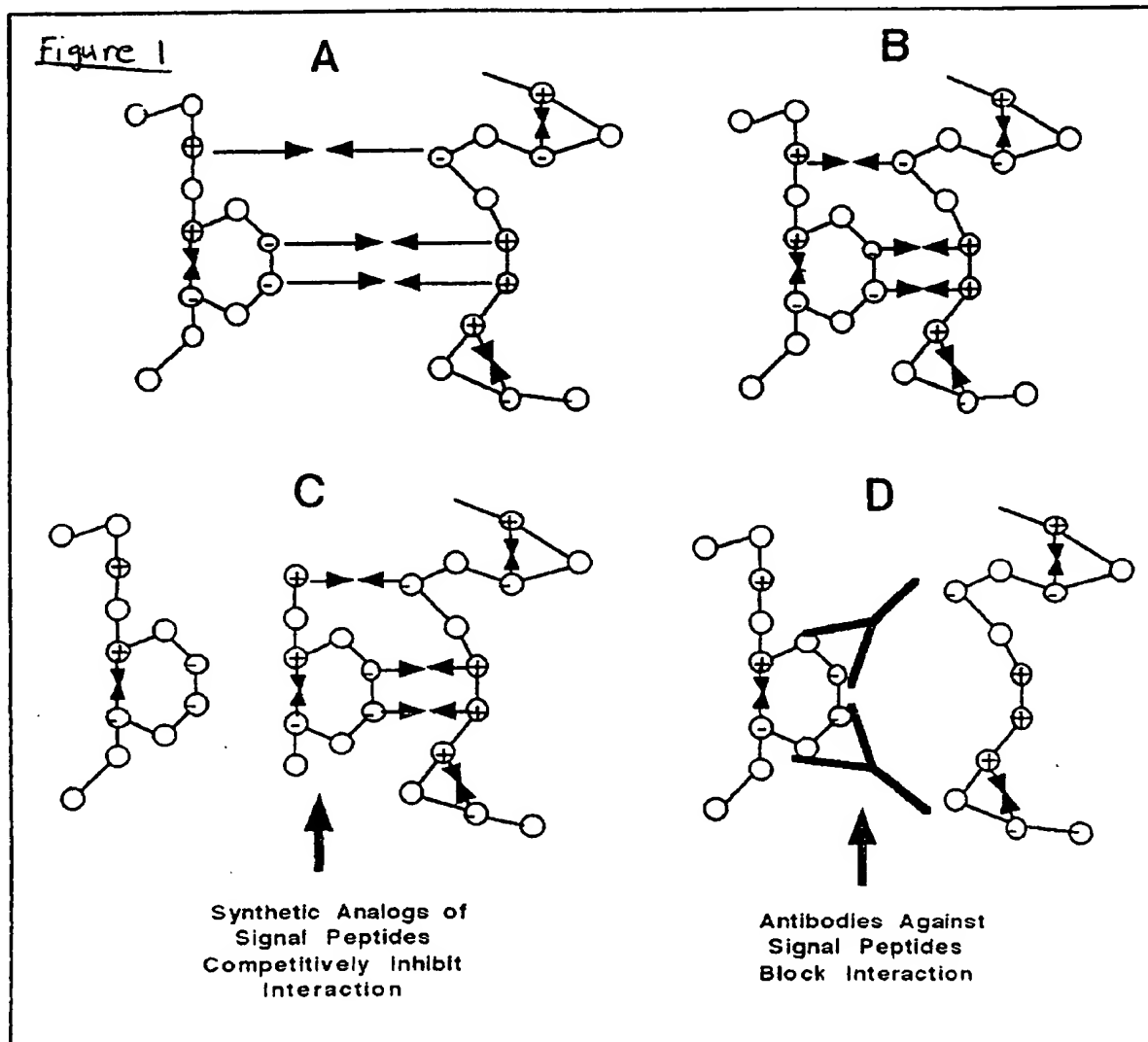• Intravenous Application

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Figure 3: Indirect Peptide Interception Therapy (Indirect PIT)

Methods for Identification, Design, Development and Therapeutic Use of Synthetic Analogs to Signal Oligopeptides in Peptide Interception Therapy as Vaccines to Stimulate a Specific Immune Response Which Decreases or Blocks Selected Protein Action

Selection of Protein in Computer Database

Identification of Hydrophylicity Maxima by Using
• Hydrophylicity Algorithm
• Surface Probability Algorithm
• Any Algorithm in Which Values Are Assigned to Amino Acid Residues in the Following Way: Charged Amino Acids > Uncharged Polar Amino Acids > Nonpolar Amino Acids
• Any Combination of the Above

Identify Signal Oligopeptides by Selecting Hydrophylicity Maxima of Protein

1

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Synthesize Synthetic Analogs to Signal Oligopeptides (Therapeutic Peptides)

Design Immunogenicity by Selecting Corresponding Xenologous Signal Oligopeptides from *Different* Species (Immunogenicity is Based on Variation of Amino Acid Residues Within Xenologous Signal Oligopeptide)

Render Therapeutic Peptides Immunogenic by Means of Haptens or Other Conventional Methods

Synthesize Synthetic Analogs to Xenologous Signal Oligopeptides (Therapeutic Peptides)

In Vitro And In Vivo Testing of Therapeutic Peptides as Vaccines Stimulating Specific Immune Response Intercepting Selected Protein Action

Test Positive

Test Negative

Clinical Testing of Therapeutic Peptides

Optimization of Therapeutic Peptide Size or Sequence by Amino Acid Residue Substitution, Deletion, Insertion etc. Testing of Analogs to Corresponding Signal Sequences from Additional Species. If Necessary, Sequence Analysis of Selected Protein from Additional Species.

Clinical Use of Indirect PIT Preferentially for, but Not Limited to
• Chronic Therapy
• Preventive Therapy
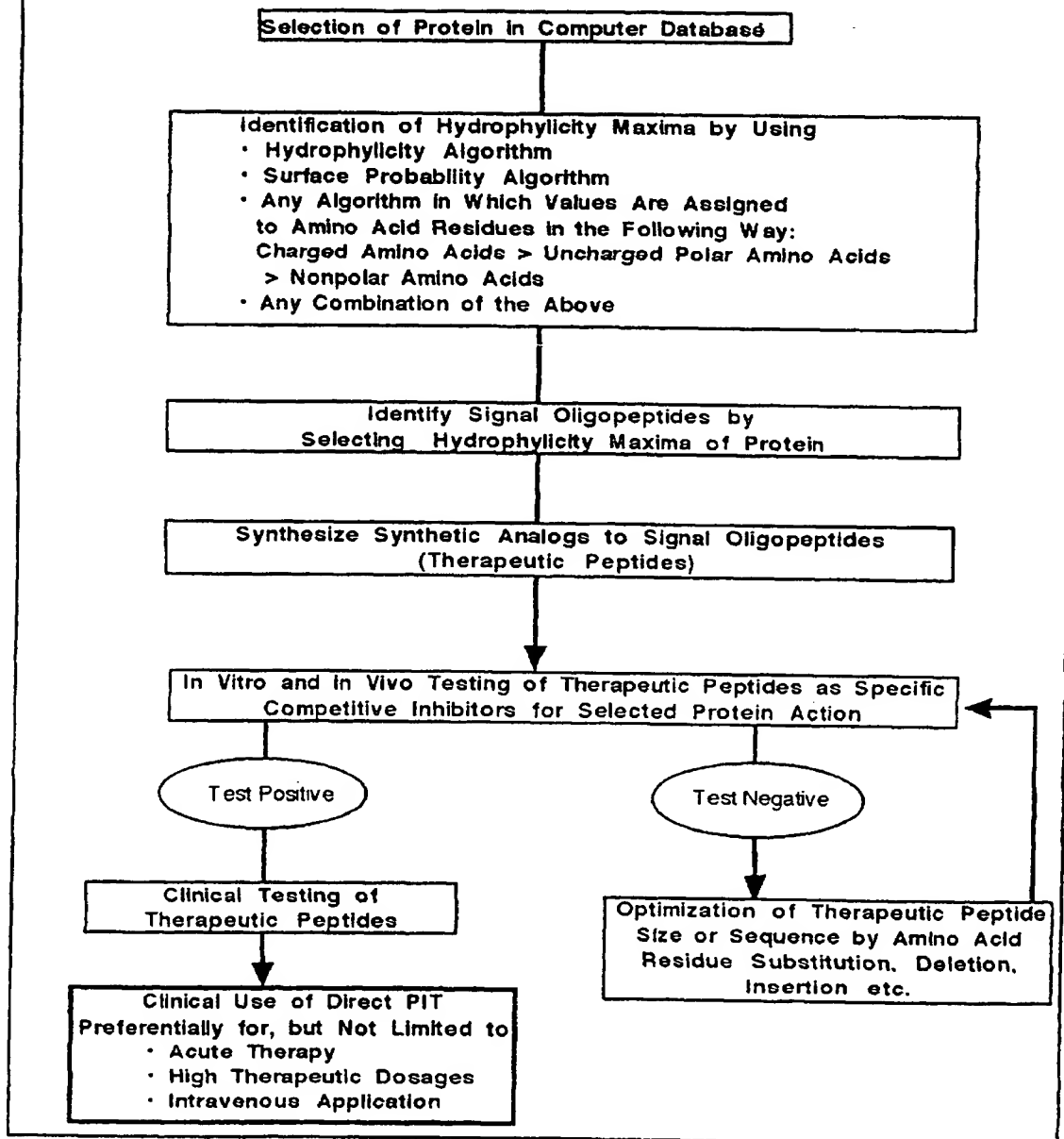• Subcutaneous Application
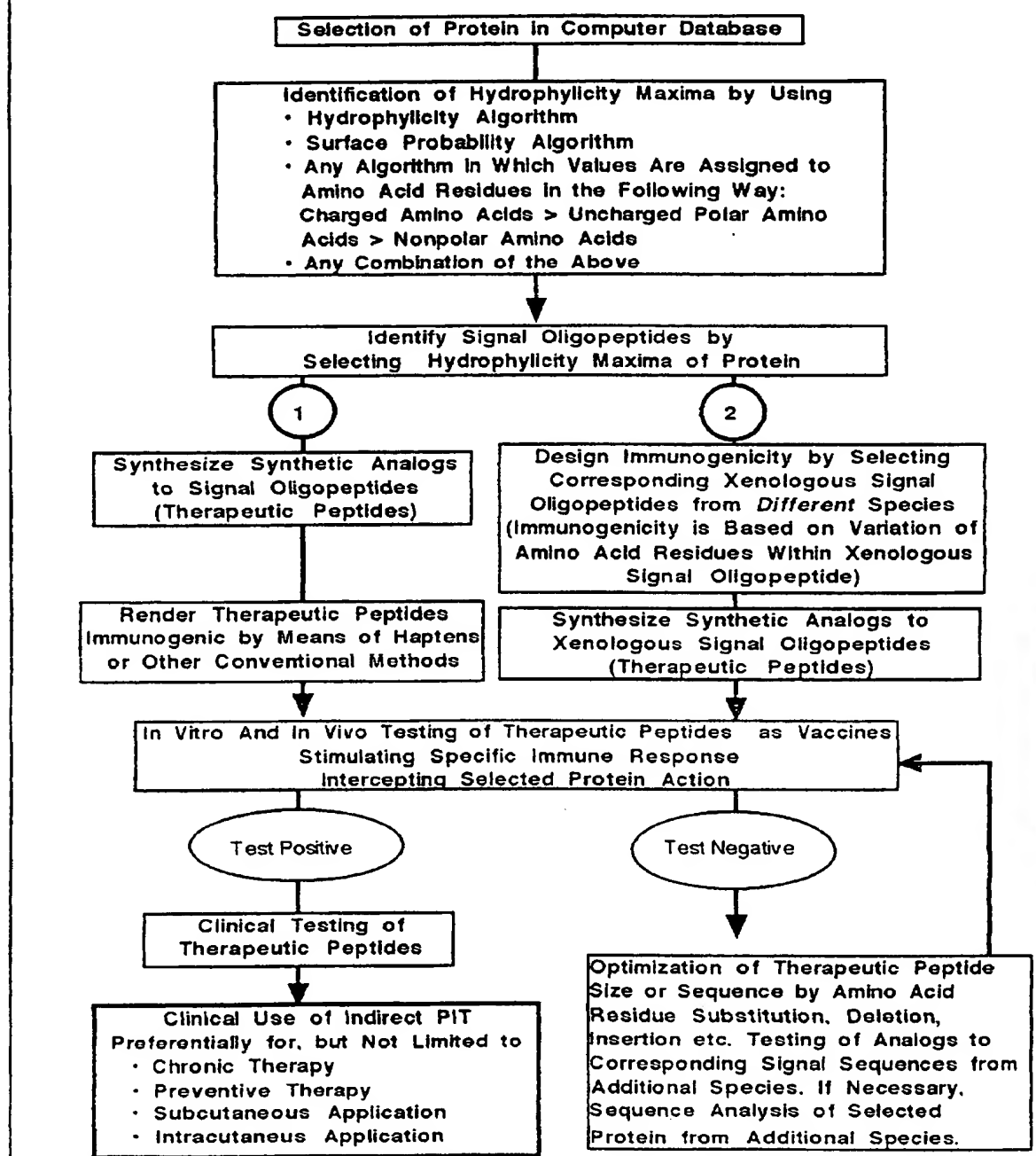• Intracutaneous Application

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Figure 4: Peptide Regulation Therapy (PRT)

Methods For Identification, Design, Development and Therapeutic Use of Synthetic Analogs to Signal Oligopeptides in Peptide Regulation Therapy as Negative Feed-Back Regulators for the Synthesis Rate of Selected Proteins

Selection of Protein In Computer Database

Identification of Hydrophylicity Maxima by Using
• Hydrophylicity Algorithm
• Surface Probability Algorithm
• Any Algorithm In Which Values Are Assigned to Amino Acid Residues in the Following Way: Charged Amino Acids > Uncharged Polar Amino Acids > Nonpolar Amino Acids
• Any Combination of the Above

Identify Signal Oligopeptides by Selecting Hydrophylicity Maxima of Protein

Synthesize Synthetic Analogs to Signal Oligopeptides (Therapeutic Peptides)

In Vitro and In Vivo Testing of Therapeutic Peptides as Negative Feed-Back Regulators for the Synthesis Rate of the Selected Protein

Test Positive

Test Negative

Clinical Testing of Therapeutic Peptides

Optimization of Therapeutic Peptide Size or Sequence by Amino Acid Residue Substitution, Deletion, Insertion etc.

Clinical Use of Peptide Regulation Therapy Preferentially for, but Not Limited to
• Acute or Chronic Therapy
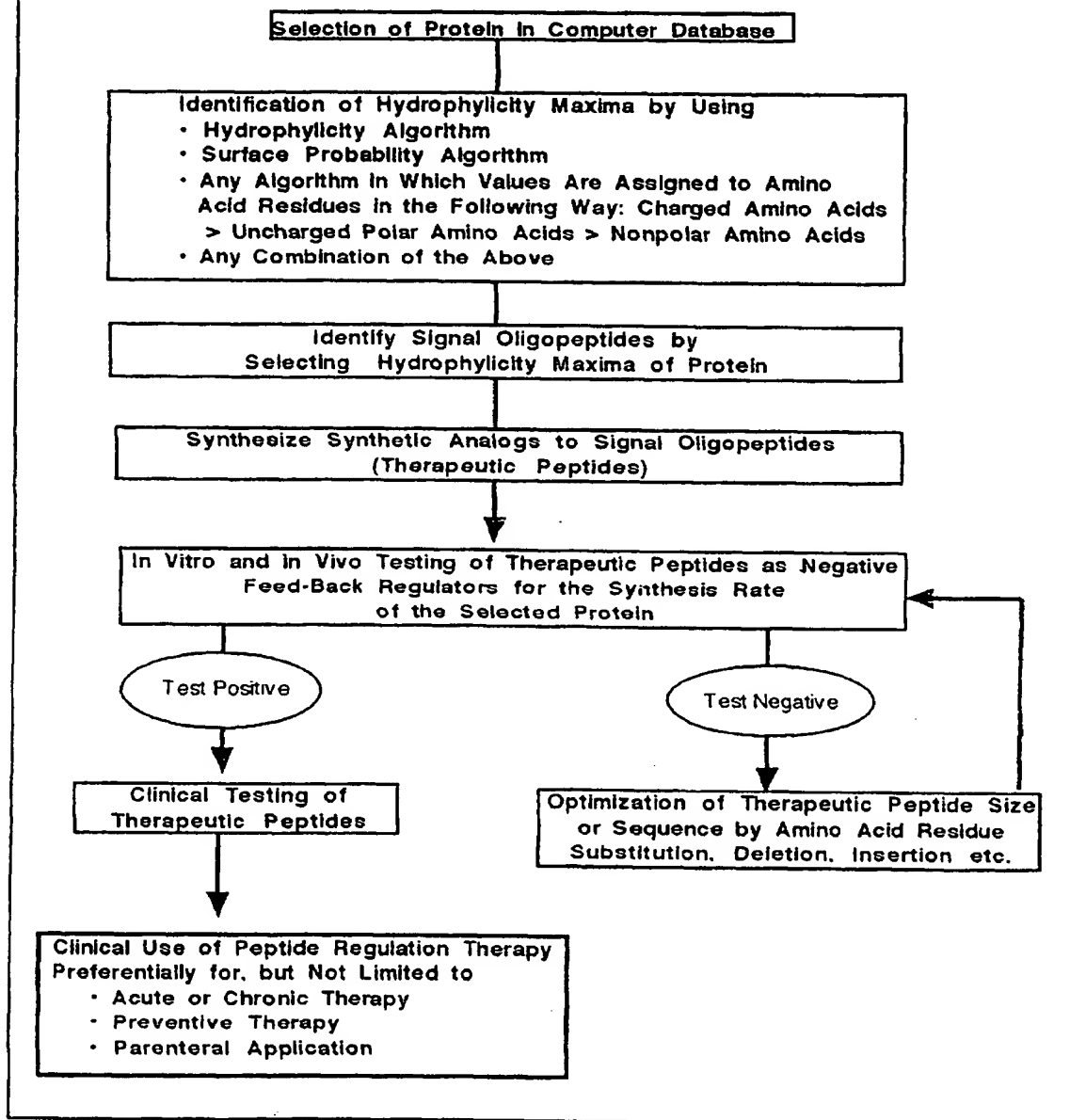• Preventive Therapy
• Parenteral Application

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Figure 5:   Amino Acid Sequence Selection and Therapeutic Design of Peptide Vaccines For Indirect Peptide Interception Therapy

Exemplified for the the Development of Glucagon Vaccines
for Indirect Peptide Interception Therapy of Diabetes Mellitus

Identify Signal Oligopeptides From Hydrophylicity Maxima From Human Glucagon Precursor Sequence
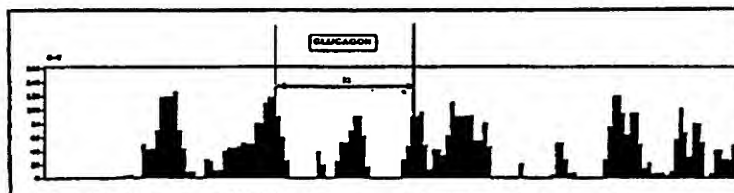
Identify Corresponding Signal Oligopeptide from Glucagon Precursor Sequences in *Different Species*

Use Evolutionary Tree to Determine Relative Distance of Available Glucagon Sequences to *Human* Sequence. The Evolutionary Distance Is Positively Correlated with Degree of Amino Acid Variation and, thus, with the Antigenicity of the Selected Protein
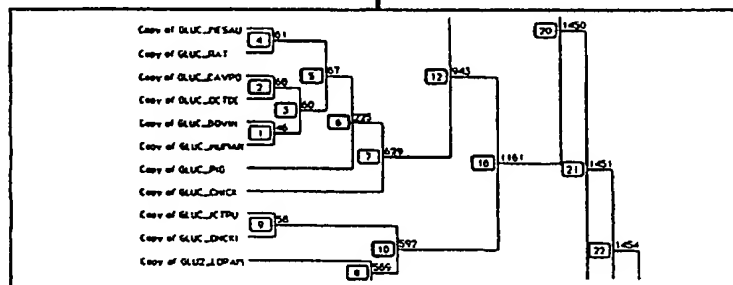
Select Therapeutic Peptide Sequence Among The
Corresponding Signal Oligopeptide Sequences
According to the Following Criteria

1.Moderate Therapeutic Immune Response Desired: Design of Therapeutic Peptides Analogous to Signal Sequences From Species Genetically Close to Humans (e.g. Mammals)
-> Amino Acid Residue Variation Within Therapeutic Peptide (Vaccine) Must Be Sufficient to Cause Immune Response
-> Therapeutic Use of Immune Response

2. Strong Therapeutic Immune Response Desired: Design of Therapeutic Peptides Analogous to Signal Sequences From Species Genetically More Distant to Humans (e.g. Fish, Yeast)
-> More Amino Acid Residue Variation Within Signal Sequence
-> Greater Antigenicity of Therap.Peptide
-> Higher Therapeutic Efficiency

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Figure 6:   Glucagon Signal Sequences And Therapeutic Use in Direct And Indirect Peptide Interception Therapy
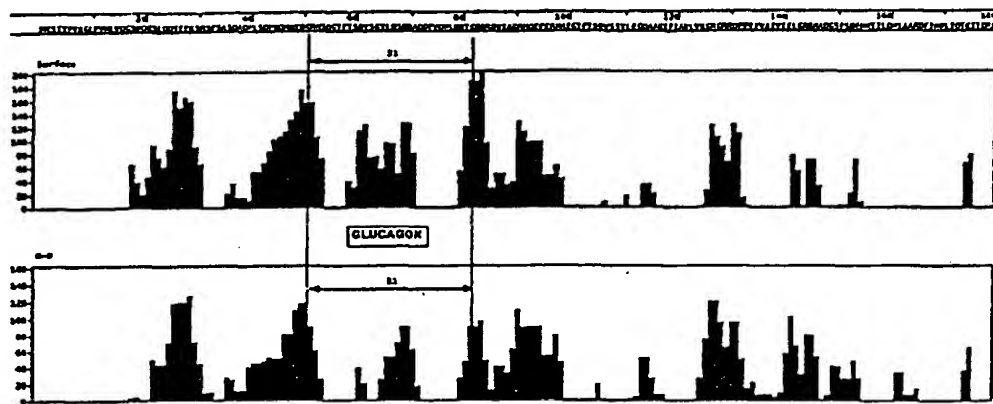
18
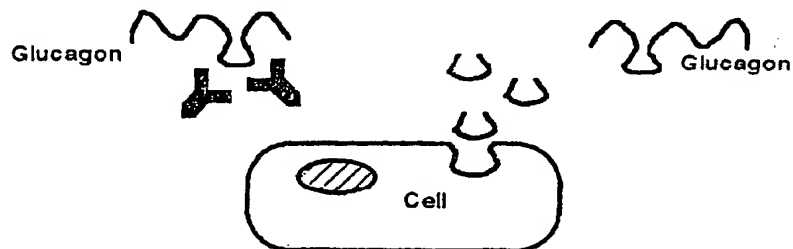
Figure 7:

Peptide Interception Therapy
in the Prevention And Treatment
of HIV Infections
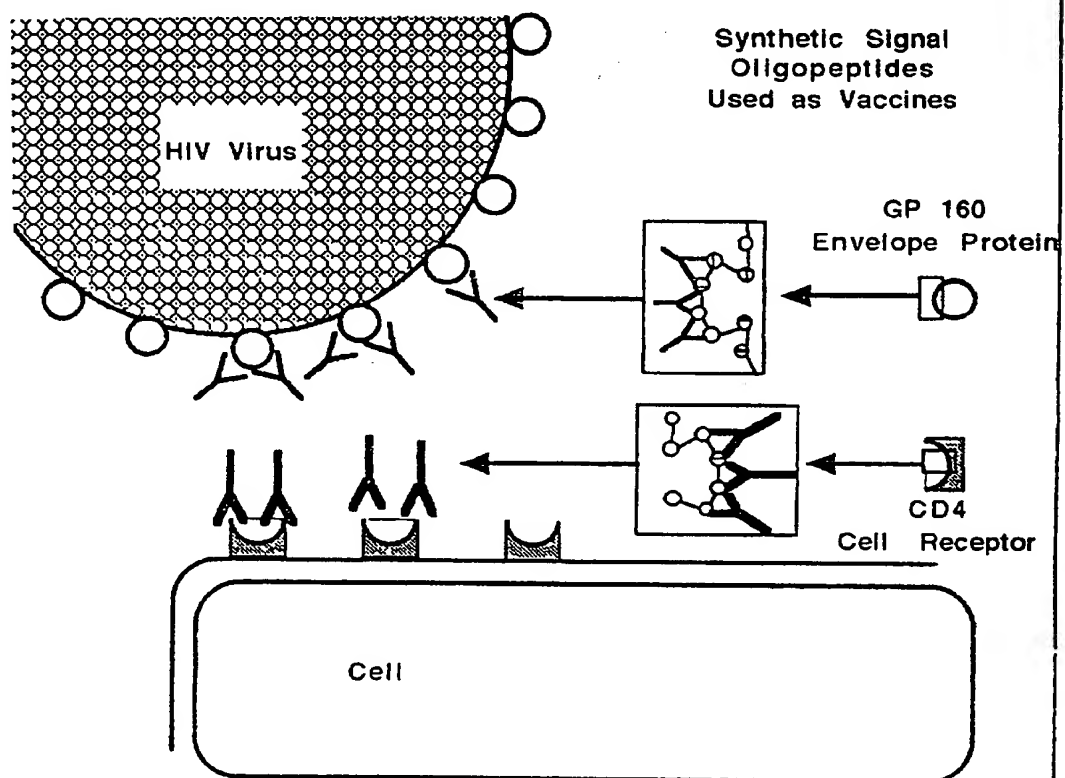
Figure 8: Signal Oligopeptides as Antigens for the Development of Highly Specific and Precisely Characterized In Vitro Diagnostic Assays

Methods For Identification, Design, Development and Use of Synthetic Analogs to Signal Oligopeptides as Antigens for the Production of Specific Antibodies with Precise Predefined Binding Characteristics

| Selection of Protein in Computer Database |

Identification of Hydrophylicity Maxima by Using
• Hydrophylicity Algorithm
• Surface Probability Algorithm
• Any Algorithm in Which Values Are Assigned to Amino Acid Residues in the Following Way: Charged Amino Acids > Uncharged Polar Amino Acids > Nonpolar Amino Acids
• Any Combination of the Above

Identify Signal Oligopeptides by Selecting Hydrophylicity Maxima of Protein

Synthesize Synthetic Analogs to Signal Oligopeptides (Antigens)

Immunization of Animals with Antigens and Production of Polyclonal and Monoclonal Antibodies According to Standard Procedures

Testing of Antibodies Against Synthetic Oligopeptide Used as Antigen and Against Entire Protein

Use of These Antibodies for the Development of Diagnostic Assays with Precise and Predefined Specificity and Epitope Characterization

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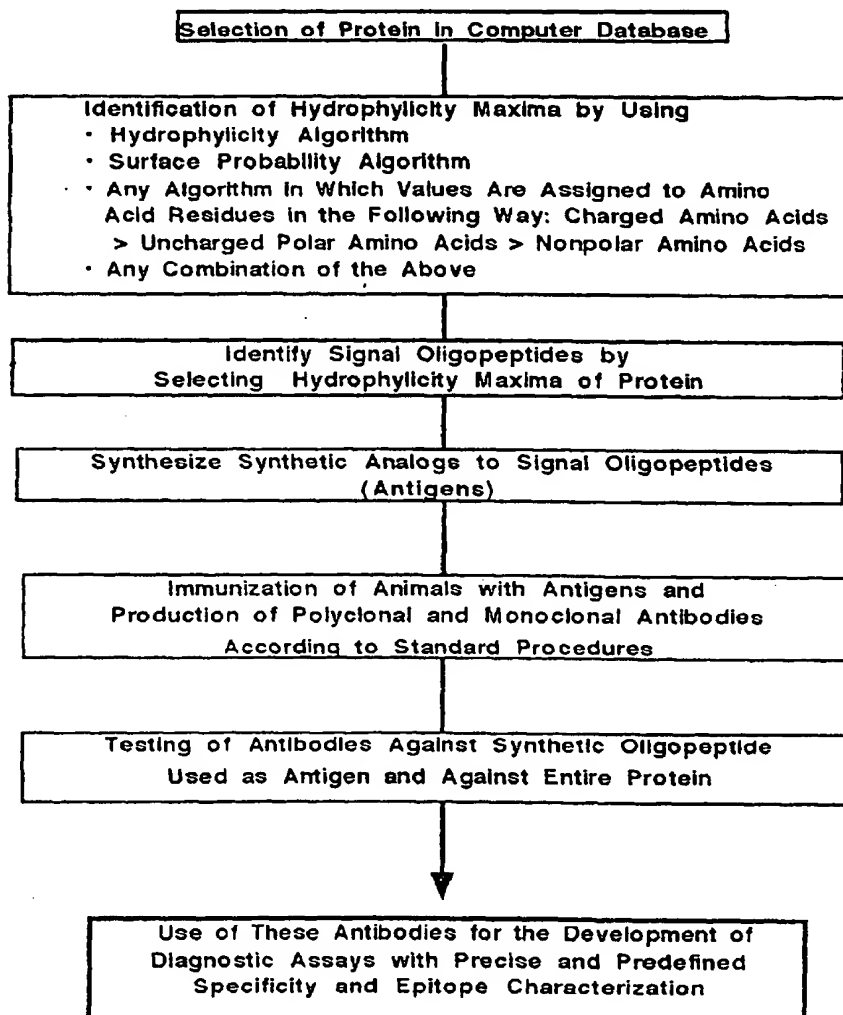| Amino Acid Residue	A. Hydrophylicity Algorithm [*]	B. Surface Probability Algorithm [**]
Arginine	3.0	9.5
Aspartate	3.0	8.1
Glutamate	3.0	8.4
Lysine	3.0	9.7
Aspartate or Asparagine	1.6	8.0
Glutamate or Glutamine	1.6	8.4
Serine	0.3	6.5
Asparagine	0.2	7.8
Glutamine	0.2	8.4
Glycine	0.0	4.8
Proline	0.0	7.5
Threonine	-0.4	7.0
Alanine	-0.5	4.9
Histidine	-0.5	6.6
Cysteine	-1.0	2.6
Methionine	-1.3	4.8
Valine	-1.5	3.6
Isoleucine	-1.8	3.4
Leucine	-1.8	4.0
Tyrosine	-2.3	7.6
Phenylalanine	-2.5	4.2
Tryptophan	-3.4	5.1

Table 1: The Maxima of the Following Algorithms -or Modifications Thereof- Can Be Used to Determine Potential Signal Oligopeptides In the Primary Structure of a Protein From a Protein Sequence Database

C. Algorithm Based on the Following Amino Acid Categories:

1. Highest Values Assigned to Charged Amino Acids:
    Aspartate, Glutamate, Lysine, Arginine, Histidine
2. Medium Values Assigned to Uncharged Polar Amino Acids:
    Asparagine, Glutamine, Glycine, Cysteine, Serine, Threonine, Tyrosine
3. Lowest Values Assigned to Non Polar Amino Acids:
    Alanine, Valine, Leucine, Isoleucine, Proline, Phenylalanine, Methionine, Tryptophan

[*]   According to Hopp TP, Woods, KR. 1981. Proc. Natl. Acad. Sci. USA, 78: 3824- 3828.
[**]   Boger. Proceedings of the 1988 Miami Bio/Technology Winter Symposium. 10 Oxford and Washington. IRL Press.

Table 2

**Methods of Use Claimed For the Signal Sequences in This Patent
And For Those in Preceding Patents
With Serial No. 07/997,734; 07/997,727; and 08/045,394**

A. Synthetic Analogs to *Human* Signal Sequences Can Be Used	B. Synthetic Analogs to Protein Signal Sequences From *Other Species* Can Be Used
1. As Therapeutic Agents for the Direct Competitive Inhibition of Selected Protein Interaction (Direct PIT)	As Therapeutic Agents (Vaccines)in the Prevention and Treatment of Human Diseases. Stimulating a Specific Immune Response Which Blocks or Decreases the Action of the Selected Protein in the Human Body.
2. As Therapeutic Agents in Feed-Back Regulation With the Therapeutic Aim to Decrease the Synthesis Rate of the Selected Protein (PRT).	2. As Therapeutic Agents According to 1 and 2 in Column A in the Treatment of Diseases in the Respective Animal Species.
3. As Therapeutic Agents In Combination With Haptens or other Conventional Immunogens or Adjuvants as Vaccines Stimulating a Specific Immune Response Which Blocks or Decreases the Action of the Selected Protein (Indirect PIT)	3. As Antigens to Produce Antibodies Against the Selected Protein for *In Vitro* Diagnostic Purposes in the Respective Animal Species.
4. As Antigens to Produce Antibodies Against the Selected Human Protein for *In Vitro* Diagnostic Purposes.	

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Table 3

The Therapeutic Use of Synthetic Signal Sequences as Vaccines
(Indirect Peptide Interception Therapy)

A. Diseases Mediated by *Xenologous* Proteins (Infectious Diseases)	B. Diseases Mediated by *Human* Proteins (e. g. Metabolic Disorders, Chronic Human Diseases)
1. Choose Signal Sequence From Xenologous Protein (e.g. Toxin) as Basis For Vaccine In Humans	1. Choose from *Different Species* the Signal Sequences Corresponding to the Selected Human Proteins (Xenologous Signal Sequence) as Basis For Vaccine
2. Use Vaccines the Prevention and Treatment of Infectious Diseases	2. Use Vaccines in the Prevention and Treatment of Metabolic Disorders, Cardiovascular Diseases and other Human Diseases

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The following specific sequences are claimed in this patent:
FARNESYL SYNTHETASE
INFORMATION FOR SEQUENCE ID NO 1
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D- V- Y- A - Q - E - K - Q - D -

INFORMATION FOR SEQUENCE ID NO 2
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - V - H - N - Q - E - K - Q - N -

INFORMATION FOR SEQUENCE ID NO 3
(A) LENGTH.
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- E - I - R - R - E - R -

INFORMATION FOR SEQUENCE ID NO 4
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY· linear
- E - D - E - M - G - H - P - E - I - G - D -

INFORMATION FOR SEQUENCE ID NO 5
(A) LENGTH·
(B) TYPE· amino acid
(D) TOPOLOGY· linear
- E - D - E - L - G - H - P - E - K - G - D -

INFORMATION FOR SEQUENCE ID NO 6
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY· linear

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-A-S-L-L-A-Y-G-M-P-K-E-

INFORMATION FOR SEQUENCE ID NO 7
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-P-R-K-Q-D-A-D-

INFORMATION FOR SEQUENCE ID NO 8
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-P-R-K-Q-D-A-E-

INFORMATION FOR SEQUENCE ID NO 9
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-N-K-T-V-E-Q-L-G-Q-E-E-

INFORMATION FOR SEQUENCE ID NO 10
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY linear
-D-D-I-M-D-S-S-L-T-R-R-

INFORMATION FOR SEQUENCE ID NO 11
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY linear
-D-D-I-M-D-S-S-Y-T-R-R-

INFORMATION FOR SEQUENCE ID NO 12
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY linear

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-D-D-M-M-D-K-S-I-T-R-R-

INFORMATION FOR SEQUENCE ID NO 13
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-K-L-Y-C-R-E-Q-P-Y-Y-

.

INFORMATION FOR SEQUENCE ID NO 14
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-K-S-H-F-R-N-E-K-Y-Y-

INFORMATION FOR SEQUENCE ID NO 15
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY. linear
-R-F-T-E-K-R-Y-K-

INFORMATION FOR SEQUENCE ID NO 16
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-Y-T-E-K-R-Y-K-

INFORMATION FOR SEQUENCE ID NO 17
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
-K-F-S-L-K-K-H-S-

INFORMATION FOR SEQUENCE ID NO 18
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY linear

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- K - V - D - L - S - K - F - S - L - K - K -

INFORMATION FOR SEQUENCE ID NO 19
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - K - H - S - F - I - V - T - F - K - T -

INFORMATION FOR SEQUENCE ID NO 20
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - G - E - K - E - H - A - N - A - K - K -

INFORMATION FOR SEQUENCE ID NO 21
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - G - E - K - E - H - A - N - A - L - K -

INFORMATION FOR SEQUENCE ID NO 22
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- T - D - E - K - D - L - K - Q - A - R - D -

INFORMATION FOR SEQUENCE ID NO 23
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY: linear
- K - I - G - T - D - I - Q - D - N - K -

INFORMATION FOR SEQUENCE ID NO 24
(A) LENGTH
(B) TYPE amino acid
(D) TOPOLOGY. linear

- K - V - G - T - D - I - Q - D - N - K -

INFORMATION FOR SEQUENCE ID NO 25
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- Q - R - A - T - P - E - Q - Y -

INFORMATION FOR SEQUENCE ID NO 26
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - R - A - T - P - Q - Q - R -

INFORMATION FOR SEQUENCE ID NO 27
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - L - A - S - A - E - Q - R -

INFORMATION FOR SEQUENCE ID NO 28
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- K - E - N - Y - G - Q - K - E - A - E - K -

INFORMATION FOR SEQUENCE ID NO 29
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - E - N - Y - G - Q - K - D - P - E - K -

INFORMATION FOR SEQUENCE ID NO 30
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear

- D - E - N - Y - G - K - K - D - S -

INFORMATION FOR SEQUENCE ID NO 31
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - V - K - A - L - Y - E - E - L -

INFORMATION FOR SEQUENCE ID NO 32
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - C - K - K - I - F - N - D - L -

INFORMATION FOR SEQUENCE ID NO 33
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - E - A - E - K - V - A - R - V - K -

INFORMATION FOR SEQUENCE ID NO 34
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear
- K - D - S - V - A - E - A - K - C - K -

INFORMATION FOR SEQUENCE ID NO 35
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- K - D - P - E - K - V - A - R -

INFORMATION FOR SEQUENCE ID NO 36
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY· linear

29

- Q - Y - E - E - D - S - Y - S - H -

INFORMATION FOR SEQUENCE ID NO 37
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - Y - E - E - D - S - Y - N - R -

INFORMATION FOR SEQUENCE ID NO 38
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - Y - E - E - S - I - A - K - D -

INFORMATION FOR SEQUENCE ID NO 39
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - K - I - Y - K - R - R - K -

INFORMATION FOR SEQUENCE ID NO 40
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY linear
- N - K - I - Y - K - R - R - K -

INFORMATION FOR SEQUENCE ID NO 41
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- N - K - V - Y - K - R - S - K -

HYDROXY-METHYL-GLUTARYL COENZYME A   REDUCTASE
INFORMATION FOR SEQUENCE ID NO 42
(A) LENGTH
(B) TYPE amino acid
(D) TOPOLOGY linear

30

-S-Q-D-E-V-R-E-N-

INFORMATION FOR SEQUENCE ID NO 43
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-T-Q-N-E-V-V-D-N-

INFORMATION FOR SEQUENCE ID NO 44
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
-E-L-S-R-E-S-R-E-G-R-

INFORMATION FOR SEQUENCE ID NO 45
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-L-S-N-S-N-K-Y-G-R-

INFORMATION FOR SEQUENCE ID NO 46
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
-R-V-L-E-E-E-E-N-K-

INFORMATION FOR SEQUENCE ID NO 47
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-V-L-E-E-E-E-D-R-K-

INFORMATION FOR SEQUENCE ID NO 48
(A) LENGTH.
(B) TYPE amino acid
(D) TOPOLOGY linear

31

- K - G - V - S - S - S - T - R - K -

INFORMATION FOR SEQUENCE ID NO 49
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- S - V - L - E - E - E - E - D - N - K -

INFORMATION FOR SEQUENCE ID NO 50
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - E - N - V - S - K - R - I - E - P -

INFORMATION FOR SEQUENCE ID NO 51
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - D - M - M - P - K - R - V - E -

INFORMATION FOR SEQUENCE ID NO 52
(A) LENGTH.
(B) TYPE amino acid
(D) TOPOLOGY: linear
- D - P - T - M - P - L - W - E - F -

INFORMATION FOR SEQUENCE ID NO 53
(A) LENGTH·
(B) TYPE· amino acid
(D) TOPOLOGY· linear
- K - K - V - P - D - N - C - C - R - R - E -

INFORMATION FOR SEQUENCE ID NO 54
(A) LENGTH
(B) TYPE. amino acid
(D) TOPOLOGY linear
- K - K - A - P - D - N - C - C - R - R - E -

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INFORMATION FOR SEQUENCE ID NO 55
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - K - Q - I - E - S - C - C - R - R - E -

INFORMATION FOR SEQUENCE ID NO 56
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- Q - K - C - D - S - V - E - E -

INFORMATION FOR SEQUENCE ID NO 57
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - K - L - S - S - V - E - E -

INFORMATION FOR SEQUENCE ID NO 58
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- H - V - S - T - T - E - E -

INFORMATION FOR SEQUENCE ID NO 59
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY linear
- E - T - L - I - S - D - Q -

INFORMATION FOR SEQUENCE ID NO 60
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY: linear
- E - E - T - G - I - N - R - E - R - K - V - E -

INFORMATION FOR SEQUENCE ID NO 61
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-E-P-G-V-S-Q-D-R-K-V-E-

INFORMATION FOR SEQUENCE ID NO 62
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-A-S-S-K-E-E-T-E-A-

INFORMATION FOR SEQUENCE ID NO 63
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear
-T-D-P-V-T-A-S-P-R-N-

INFORMATION FOR SEQUENCE ID NO 64
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear
-E-P-E-I-E-L-P-R-E-P-R-P-N-E-E-

INFORMATION FOR SEQUENCE ID NO 65
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-L-E-I-E-L-P-S-E-P-R-P-N-E-E-

INFORMATION FOR SEQUENCE ID NO 66
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear
-N-T-M-F-D-L-P-E-E-P-R-P-L-D-E-

INFORMATION FOR SEQUENCE ID NO 67
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - V - E - W - V - L - E - T - E - L - K - A - P - R - P -

INFORMATION FOR SEQUENCE ID NO 68
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - E - P - R - P - N - E - E - C -

INFORMATION FOR SEQUENCE ID NO 69
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - L - K - A - P - R - P - M -

INFORMATION FOR SEQUENCE ID NO 70
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - E - P - R - P - L - D - E - C -

INFORMATION FOR SEQUENCE ID NO 71
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY: linear
- H - E - R - G - U - S - I - R - R - Q - L - L - S - K - K -

INFORMATION FOR SEQUENCE ID NO 72
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- P - R - E - G - V - A - I - R - R - Q - M - L - S - D - K -

INFORMATION FOR SEQUENCE ID NO 73
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- P - E - R - G - V - A - V - R - R - Q - I - I - S - K -

INFORMATION FOR SEQUENCE ID NO 74
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- P - F - R - A - V - E - L - R - R - L - D - L -

INFORMATION FOR SEQUENCE ID NO 75
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - Q - Y - L - P - Y - R - D - Y - N -

INFORMATION FOR SEQUENCE ID NO 76
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY. linear
- I - E - R - I - P - Y - K - D - Y - D -

INFORMATION FOR SEQUENCE ID NO 77
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - Q - S - L - P - Y - K - N - Y - N -

INFORMATION FOR SEQUENCE ID NO 78
(A) LENGTH:
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- L - E - K - L - P - Y - A - S - Y - D -

36

INFORMATION FOR SEQUENCE ID NO 79
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- C - L - D - E - K - E - F - Q -

INFORMATION FOR SEQUENCE ID NO 80
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- C - L - D - G - K - E - Y - Q -

INFORMATION FOR SEQUENCE ID NO 81
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - L - N - N - K - E - Y - Q -

INFORMATION FOR SEQUENCE ID NO 82
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - L - D - G - Q - E - F - Q -

INFORMATION FOR SEQUENCE ID NO 83
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - L - D - G - R - S - H - Y -

INFORMATION FOR SEQUENCE ID NO 84
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - L - P - R - A - C - D - S - A - E - V - K -

INFORMATION FOR SEQUENCE ID NO 85
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - L - P - T - A - C - D - A - A - E - V - K -

INFORMATION FOR SEQUENCE ID NO 86
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - L - P - S - A - Q - E - A - G - A - I - K -

INFORMATION FOR SEQUENCE ID NO 87
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - K - A - L - S - K - L - H - E - Y -

INFORMATION FOR SEQUENCE ID NO 88
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- E - K - A - L - V - K - L - Q - E - F -

INFORMATION FOR SEQUENCE ID NO 89
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - Q - A - L - A - R - L - Q - E - E -

INFORMATION FOR SEQUENCE ID NO 90
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - Q - A - L - H - A - L - Q - T - M -

INFORMATION FOR SEQUENCE ID NO 91
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-C-K-D-N-P-G-E-N-A-R-

INFORMATION FOR SEQUENCE ID NO 92
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-S-T-E-T-P-G-K-N-A-C-

INFORMATION FOR SEQUENCE ID NO 93
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-N-I-H-G-S-G-L-N-A-S-

INFORMATION FOR SEQUENCE ID NO 94
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-N-R-S-K-I-N-L-Q-D-

INFORMATION FOR SEQUENCE ID NO 95
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-N-R-S-A-L-N-I-D-E-

GLUCAGON   PRECURSOR
INFORMATION FOR SEQUENCE ID NO 96
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear

-D-Y-S-K-Y-L-D-S-

INFORMATION FOR SEQUENCE ID NO 97
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-S-R-R-A-Q-D-

INFORMATION FOR SEQUENCE ID NO 98
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-Y-S-K-Y-L-D-S-R-R-A-Q-D-

INFORMATION FOR SEQUENCE ID NO 99
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-V-A-S-L-T-D-Y-L-K-S-K-R-

INFORMATION FOR SEQUENCE ID NO 100
(A) LENGTH.
(B) TYPE. amino acid
(D) TOPOLOGY linear
-D-Y-S-K-Y-M-D-N-R-R-A-K-D-

INFORMATION FOR SEQUENCE ID NO 101
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-Y-S-K-Y-L-D-N-R-R-A-K-D-

INFORMATION FOR SEQUENCE ID NO 102
(A) LENGTH.
(B) TYPE. amino acid
(D) TOPOLOGY· linear
-D-Y-S-K-Y-L-D-S-R-R-A-Q-Q-

INFORMATION FOR SEQUENCE ID NO 103
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - Y - L - D - S -

INFORMATION FOR SEQUENCE ID NO 104
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - S - R - R - A - Q - D -

INFORMATION FOR SEQUENCE ID NO 105
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - Y - L - D - S - R - R - A - Q - D -

INFORMATION FOR SEQUENCE ID NO 106
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY linear
- D - V - A - S - L - T - D - Y - L - K - S - K - R -

INFORMATION FOR SEQUENCE ID NO 107
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - Y - M - D - N - R - R - A - K - D -

INFORMATION FOR SEQUENCE ID NO 108
(A) LENGTH
(B) TYPE amino acid
(D) TOPOLOGY linear
- D - Y - S - K - Y - L - D - N - R - R - A - K - D -

INFORMATION FOR SEQUENCE ID NO 109
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - Y - L - D - S - R - R - A - Q - Q -

INFORMATION FOR SEQUENCE ID NO 110
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - F - L - D - T - R - R - A - Q - D -

INFORMATION FOR SEQUENCE ID NO 111
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - Y - Q - E - E - R - M - A - Q - D -

INFORMATION FOR SEQUENCE ID NO 112
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - S - K - Y - L - E - T - R - R - A - Q - D -

INFORMATION FOR SEQUENCE ID NO 113
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- D - Y - S - K - Y - L - D - N - R - R - T - K - D -

INFORMATION FOR SEQUENCE ID NO 114
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- D - M - S - S - Y - L - E - E - K - A - A - K - E -

42

INFORMATION FOR SEQUENCE ID NO 115
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - F - N - K - A - L - D - I - K - A - A - Q - E -

INFORMATION FOR SEQUENCE ID NO 116
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - P - L - S - D - P - D - Q - M -

INFORMATION FOR SEQUENCE ID NO 117
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- N - E - D - K - R - H - S - Q -

INFORMATION FOR SEQUENCE ID NO 118
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - D - E - P - R - E - L - S - N - M - K - R - H - S - E -

INFORMATION FOR SEQUENCE ID NO 119
(A) LENGTH.
(B) TYPE. amino acid
(D) TOPOLOGY: linear
- R - E - L - S - N - M - K - R - H -

INFORMATION FOR SEQUENCE ID NO 120
(A) LENGTH
(B) TYPE. amino acid
(D) TOPOLOGY linear
- E - A - R - E - L - S - T - P - K - X - H - S - E -

43

INFORMATION FOR SEQUENCE ID NO 121
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - D - P - D - Q - I - N - E - D - K - R - H -

INFORMATION FOR SEQUENCE ID NO 122
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - D - P - D - Q - M - N - E - D - K - R - H - S - Q -

INFORMATION FOR SEQUENCE ID NO 123
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- G - D - P - D - Q - I - N - E - D - K - R - H - S - Q -

INFORMATION FOR SEQUENCE ID NO 124
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - E - S - R - Q - L - N - E - V - K - R - H - S - Q -

INFORMATION FOR SEQUENCE ID NO 125
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- M - N - T - K - R - N - R - N - N -

INFORMATION FOR SEQUENCE ID NO 126
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear

- K - R - H - D - E - F - E - R - H -

INFORMATION FOR SEQUENCE ID NO 127
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- M - N - T - K - R - N - R - N - R - N - N - K - R - H - D - E - F - E - R - H -

INFORMATION FOR SEQUENCE ID NO 128
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- N - K - R - S - G - V - A - E - K - R -

INFORMATION FOR SEQUENCE ID NO 129
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- V - K - R - N - R - N - N - I - A - K - R -

INFORMATION FOR SEQUENCE ID NO 130
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- K - N - T - K - R - N - R - N - E -

INFORMATION FOR SEQUENCE ID NO 131
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- T - K - R - N - G - O - O - G - Q - E - D - K -

INFORMATION FOR SEQUENCE ID NO 132
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY. linear
- Q - E - D - K - E - N - D - K - F -

45

INFORMATION FOR SEQUENCE ID NO 133
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - R - H - S - E - F - E - R - H - A - E -

INFORMATION FOR SEQUENCE ID NO 134
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- Q - D - T - E - E - K - S - R -

INFORMATION FOR SEQUENCE ID NO 135
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- Q - D - T - E - E - K - P - R -

INFORMATION FOR SEQUENCE ID NO 136
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- Q - D - T - E - E - N - A - R -

INFORMATION FOR SEQUENCE ID NO 137
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- D - Q - D - P - D - R - N - S - M -

INFORMATION FOR SEQUENCE ID NO 138
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY linear
- K - G - R - G - R - R - D - F - P - E - E -

INFORMATION FOR SEQUENCE ID NO 139
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - R - L - K - A - Q - V - R - R - E -

INFORMATION FOR SEQUENCE ID NO 140
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - K - L - K - S - G - K - V -

INFORMATION FOR SEQUENCE ID NO 141
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - S - G - Q - P - K - P - E -

INFORMATION FOR SEQUENCE ID NO 142
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - Q - G - Q - D - R - R - E -

GASTRIN   PRECURSOR
INFORMATION FOR SEQUENCE ID NO 143
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - D - P - S - K - K - Q -

INFORMATION FOR SEQUENCE ID NO 144
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY. linear
- R - T - D - L - S - K - K - Q -

INFORMATION FOR SEQUENCE ID NO 145
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - D - L - S - K - K - Q -

INFORMATION FOR SEQUENCE ID NO 146
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - L - S - K - K - Q - R -

INFORMATION FOR SEQUENCE ID NO 147
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- W - L - E - E - E - E - A -

INFORMATION FOR SEQUENCE ID NO 148
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear
- W - M - E - E - E - E - A -

INFORMATION FOR SEQUENCE ID NO 149
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- W - V - E - E - E - E - A -

INFORMATION FOR SEQUENCE ID NO 150
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- W - A - E - E - E - E - A -

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INFORMATION FOR SEQUENCE ID NO 151
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- P - M - E - E - E - E - A -

INFORMATION FOR SEQUENCE ID NO 152
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - F - G - R - R - S - A - E - D - E - N -

INFORMATION FOR SEQUENCE ID NO 153
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- M - D - F - G - R - R - S -

INFORMATION FOR SEQUENCE ID NO 154
(A) LENGTH·
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- R - R - S - A - E - D - E -

INFORMATION FOR SEQUENCE ID NO 155
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - R - S - A - E - D - G - D - Q - H - P -

INFORMATION FOR SEQUENCE ID NO 156
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - D - L - E - L - P - W - L - E -

49

INFORMATION FOR SEQUENCE ID NO 157
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - G - K - E - P - H - E - L - D - R -

INFORMATION FOR SEQUENCE ID NO 158
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - G - Q - E - P - L - R -

INFORMATION FOR SEQUENCE ID NO 159
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - P - H - W - L - N - R -

INFORMATION FOR SEQUENCE ID NO 160
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - P - R - S - Q - Q - P - D -

INFORMATION FOR SEQUENCE ID NO 161
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - P - G - F - Q - L - Q - D -

INFORMATION FOR SEQUENCE ID NO 162
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - P - H - S - H - L - Q - D -

50

INFORMATION FOR SEQUENCE ID NO 163
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - P - R - S - Q - L - Q - D -

GONADOLIBERIN PRECURSOR
INFORMATION FOR SEQUENCE ID NO 164
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- Q - H - W - S - Y - G - L - R - P - G - G - K -

INFORMATION FOR SEQUENCE ID NO 165
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- G - L - Q - P - G - G - K - R - D -

INFORMATION FOR SEQUENCE ID NO 166
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- H - G - W - L - P - G - G - K - R - D -

INFORMATION FOR SEQUENCE ID NO 167
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- G - W - L - P - G - G - K - R - D -

INFORMATION FOR SEQUENCE ID NO 168
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear

51

-H-G-W-Y-P-G- G-K-R-D-

INFORMATION FOR SEQUENCE ID NO 169
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-Q-H-Y-S-L-E-W-K-P-G-

INFORMATION FOR SEQUENCE ID NO 170
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-P-G-G-K-R-D-A-E-

INFORMATION FOR SEQUENCE ID NO 171
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-P-G-G-K-R-N-T-E-H-

INFORMATION FOR SEQUENCE ID NO 172
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-Q-P-G-G-K-R-D-A-E-

PLASMINOGEN   ACTIVATOR   INHIBITOR   1
INFORMATION FOR SEQUENCE ID NO 173
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-Q-A-S-K-D-R-

INFORMATION FOR SEQUENCE ID NO 174
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear

-K-I-D-D-K-G-.

INFORMATION FOR SEQUENCE ID NO 175
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-W-N-K-D-E-

INFORMATION FOR SEQUENCE ID NO 176
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-V-E-R-A-R-

INFORMATION FOR SEQUENCE ID NO 177
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-R-R-L-F-H-K-S-D-

INFORMATION FOR SEQUENCE ID NO 178
(A) LENGTH:
(B) TYPE· amino acid
(D) TOPOLOGY: linear
-K-T-P-F-P-D-S-

INFORMATION FOR SEQUENCE ID NO 179
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-Y-E-K-E-V-P-

INFORMATION FOR SEQUENCE ID NO 180
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY linear
-E-V-D-L-R-K-P-

53

INFORMATION FOR SEQUENCE ID NO 181
(A.) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - V - K - I - E - V - N - E -

INFORMATION FOR SEQUENCE ID NO 182
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - R - M - A - P - E - E -

INFORMATION FOR SEQUENCE ID NO 183
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - A - S - K - D - R -

INFORMATION FOR SEQUENCE ID NO 184
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - I - E - E - K - G -

INFORMATION FOR SEQUENCE ID NO 185
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - V - N - E - K - G -

INFORMATION FOR SEQUENCE ID NO 186
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY: linear
- N - I - S - E - R - G -

54

INFORMATION FOR SEQUENCE ID NO 187
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- W - N - K - N - E -

INFORMATION FOR SEQUENCE ID NO 188
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - M - P - F - P - E - S -

INFORMATION FOR SEQUENCE ID NO 189
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - T - P - F - L - E - A -

INFORMATION FOR SEQUENCE ID NO 190
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- H - H - R - L - F - H - K - S - D -

INFORMATION FOR SEQUENCE ID NO 191
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- H - Q - R - L - F - H - K - S - D -

INFORMATION FOR SEQUENCE ID NO 192
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - V - D - L - R - G - P - L - E - K -

55

INFORMATION FOR SEQUENCE ID NO 193
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - I - D - L - R - R - P - L - E -

INFORMATION FOR SEQUENCE ID NO 194
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - R - M - A - P - T - E - M -

PLASMINOGEN   ACTIVATOR   INHIBITOR 2
INFORMATION FOR SEQUENCE ID NO 195
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - W - K - T - P - F - E - K -

INFORMATION FOR SEQUENCE ID NO 196
(A) LENGTH
(B) TYPE. amino acid
(D) TOPOLOGY· linear
- R - E - K - L - N - I - G - Y - I - E - D - L - K -

INFORMATION FOR SEQUENCE ID NO 197
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- H - A - K - L - N - I - G - Y - I - K - D - L - K -

INFORMATION FOR SEQUENCE ID NO 198
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear

- K - D - K - M - A - E - D - E - V - E -

INFORMATION FOR SEQUENCE ID NO 199
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - D - T - L - D - E - D - D -

INFORMATION FOR SEQUENCE ID NO 200
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - L - E - E - H - Y - E - L - R -

INFORMATION FOR SEQUENCE ID NO 201
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- K - L - A - Q - S - Y - E - L - K -

INFORMATION FOR SEQUENCE ID NO 202
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY: linear
- E - R - N - D - L - F - L - S - E -

INFORMATION FOR SEQUENCE ID NO 203
(A) LENGTH
(B) TYPE amino acid
(D) TOPOLOGY: linear
- D - V - N - E - E - G - T - E -

INFORMATION FOR SEQUENCE ID NO 204
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - V - T - E - E - G - T - V -

INFORMATION FOR SEQUENCE ID NO 205
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - G - S - T - E - D - E - Q -

INFORMATION FOR SEQUENCE ID NO 206
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- G - G - N - T - E - Q - Q -

INFORMATION FOR SEQUENCE ID NO 207
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - K - S - A - S - F - R - E - E -

INFORMATION FOR SEQUENCE ID NO 208
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- E - K - S - A - R - F - K - E - E -

INFORMATION FOR SEQUENCE ID NO 209
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - E - A - R - K - K -

INFORMATION FOR SEQUENCE ID NO 210
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- E - E - A - R - E - K -

58

INFORMATION FOR SEQUENCE ID NO 211
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - T - Q - T - K - G - K -

INFORMATION FOR SEQUENCE ID NO 212
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - T - Q - T - K - G - E -

INFORMATION FOR SEQUENCE ID NO 213
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - G - S - V - D - G - D - T - R -

INFORMATION FOR SEQUENCE ID NO 214
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - G - S - V - D - E - D - T - K -

ALZHEIMER AMYLOID A4
INFORMATION FOR SEQUENCE ID NO 215
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - S - A - D - A - E - E - D - D -

INFORMATION FOR SEQUENCE ID NO 216
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear

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- E - E - E - E - V - A - E - V -E -

INFORMATION FOR SEQUENCE ID NO 217
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - E - E - E - A - D - D - D -

INFORMATION FOR SEQUENCE ID NO 218
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
A - D - D - D - E - D - D- E - D - G -

INFORMATION FOR SEQUENCE ID NO 219
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - E - D - G - D - E - V - E -

INFORMATION FOR SEQUENCE ID NO 220
(A) LENGTH:
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- E - E - A - E - E - P - Y - E - E -

INFORMATION FOR SEQUENCE ID NO 221
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - D - V - E - E - E - E - A - D - D - D - E - D - V - E -

INFORMATION FOR SEQUENCE ID NO 222
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - A - K - E - R - L - E -

INFORMATION FOR SEQUENCE ID NO 223
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - A - K - H - R - E - R -

INFORMATION FOR SEQUENCE ID NO 224
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - E - W - E - E - A - E - R -

INFORMATION FOR SEQUENCE ID NO 225
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - A - E - Q - K - D - R -

APOLIPOPROTEIN E
INFORMATION FOR SEQUENCE ID NO 226
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- E - P - E - T - E - P - D - V - R -

INFORMATION FOR SEQUENCE ID NO 227
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY linear
- E - G - E - P - E - V - T - D -

INFORMATION FOR SEQUENCE ID NO 228
(A) LENGTH
(B) TYPE amino acid
(D) TOPOLOGY. linear

61

-E-T-E-P-E-P-E-L-R-

INFORMATION FOR SEQUENCE ID NO 229
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-D-V-C-G-R-

INFORMATION FOR SEQUENCE ID NO 230
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-D-V-R-G-R-

INFORMATION FOR SEQUENCE ID NO 231
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-D-L-R-N-R-

INFORMATION FOR SEQUENCE ID NO 232
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-L-R-K-L-R-K-R-

INFORMATION FOR SEQUENCE ID NO 233
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-P-R-K-M-K-R-R-

INFORMATION FOR SEQUENCE ID NO 234
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-L-R-K-M-R-K-R-

62

INFORMATION FOR SEQUENCE ID NO 235
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - D - R - L - D - E - V - K - E -

INFORMATION FOR SEQUENCE ID NO 236
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - A - R - M - E - E -

INFORMATION FOR SEQUENCE ID NO 237
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - G - R - M - E - E -

INFORMATION FOR SEQUENCE ID NO 238
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY linear
- R - G - R - L - E - E -

HERPES VIRUS 1 (HSV1) GLYCOPROTEIN B
INFORMATION FOR SEQUENCE ID NO 239
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - T - E - V - Q - R - R - N - Q - L - H - D -

INFORMATION FOR SEQUENCE ID NO 240
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY linear

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-K-E-L-K-N-P-T-N-P-D-

INFORMATION FOR SEQUENCE ID NO 242
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-G-E-E-G-G-D-F-D-E-A-K-

INFORMATION FOR SEQUENCE ID NO 242
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-E-A-K-L-A-E-A-R-E-M-I-R-

INFORMATION FOR SEQUENCE ID NO 243
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-M-V-M-R-K-R-R-N-

INFORMATION FOR SEQUENCE ID NO 244
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-K-R-R-N-T-N-Y-T-Q-V-P-N-K-D-A-D-E-D-D-L-

HERPES VIRUS 2 (HSV 23, 2H) GLYCOPROTEIN B
INFORMATION FOR SEQUENCE ID NO 245
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-K-A-R-K-R-K-T-K-K-

INFORMATION FOR SEQUENCE ID NO 246
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear

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-K-K-P-P-K-R-P-E-

INFORMATION FOR SEQUENCE ID NO 247
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-D-A-R-E-A-I-D-R-

INFORMATION FOR SEQUENCE ID NO 248
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-E-Y-M-R-E-Q-D-R-K-

INFORMATION FOR SEQUENCE ID NO 249
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-K-R-N-K-A-R-

INFORMATION FOR SEQUENCE ID NO 250
(A) LENGTH·
(B) TYPE· amino acid
(D) TOPOLOGY: linear
-E-D-E-A-G-D-E-D-E-L-

INFORMATION FOR SEQUENCE ID NO 251
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-K-R-N-K-A-R-Y-S-P-L-H-N-E-D-E-A-G-D-E-D-E-L-

TREPONEMA PALLIDUM MEMBRANE PROTEIN TMPA
INFORMATION FOR SEQUENCE ID NO 252
(A) LENGTH·
(B) TYPE amino acid
(D) TOPOLOGY· linear

- K - E - E - A - E - K - K - A - A - E - Q - R -

INFORMATION FOR SEQUENCE ID NO 253
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- H - A - D - R - R - L - M - E -

INFORMATION FOR SEQUENCE ID NO 254
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - V - E - R - Q - S - T - D - A - K -

INFORMATION FOR SEQUENCE ID NO 255
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - I - E - G - D - L - K - K -

INFORMATION FOR SEQUENCE ID NO 256
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - L - R - P - Q - L - E - E - A - D -

INFORMATION FOR SEQUENCE ID NO 257
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - S - Q - Y - Q - E - A - R - E - A - E - E -

INFORMATION FOR SEQUENCE ID NO 258
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - L - K - K - T - E - A - E - K -

INFORMATION FOR SEQUENCE ID NO 259
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- A - K - T - K - Q - K - A -

INFORMATION FOR SEQUENCE ID NO 260
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - L - A - R - S - A - D - K - S -

INFORMATION FOR SEQUENCE ID NO 261
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - E - P - I - E - V - E - P - L - P - N - D - R -

INFORMATION FOR SEQUENCE ID NO 262
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- R - V - Q - S - R - G - V - E - D - G - G - R - S - P - K -

ISLET AMYLOID POLYPEPTIDE
INFORMATION FOR SEQUENCE ID NO 263
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - S - H - Q - V - E - K - R - K -

INFORMATION FOR SEQUENCE ID NO 264
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- N - P - Q - M - D - K - R - K -

INFORMATION FOR SEQUENCE ID NO 265
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - H - R - V - D - K - R - K -

INFORMATION FOR SEQUENCE ID NO 266
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - R - N - A - V - E - V - L - K - R - E -

INFORMATION FOR SEQUENCE ID NO 267
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - R - N - V - A - E - D - P - N - R - E -

INFORMATION FOR SEQUENCE ID NO 268
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - R - N - A - E - V - V - D - V - E -

COLLAGENASE   (FIBROBLAST   MMP1)
INFORMATION FOR SEQUENCE ID NO 269
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- L - K - N - D - G - R - Q - V - E - K - R - R - N -

INFORMATION FOR SEQUENCE ID NO 270
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear

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- K - N - D - G - R - Q - V - E - K - R - R -

INFORMATION FOR SEQUENCE ID NO 271
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - D - D - W - R - K - I - P - K - Q - R -

INFORMATION FOR SEQUENCE ID NO 272
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - K - V - E - R - Q - R -

INFORMATION FOR SEQUENCE ID NO 273
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - G - V - P - V - E - K - K - R -

INFORMATION FOR SEQUENCE ID NO 274
(A) LENGTH.
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- R - G - D - H - R - D - N -

INFORMATION FOR SEQUENCE ID NO 275
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY. linear
- D - E - H - E - R - W -

INFORMATION FOR SEQUENCE ID NO 276
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- D - E - D - D - R - W - T - K - D -

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INFORMATION FOR SEQUENCE ID NO 277
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - F - A - D - R - D - E - V - R -

INFORMATION FOR SEQUENCE ID NO 278
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - V - A - H - R - D - E -

INFORMATION FOR SEQUENCE ID NO 279
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - V - A - D - R - D - E - V - R -

INFORMATION FOR SEQUENCE ID NO 280
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - Y - D - E - Y - K - R -

SCHISTOSOMA ELASTASE PRECURSOR
INFORMATION FOR SEQUENCE ID NO 281
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - S - G - E - P -

INFORMATION FOR SEQUENCE ID NO 282
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - N - G - D - Q - Q - G - I - H - H -

INFORMATION FOR SEQUENCE ID NO 283

(A) LENGTH:

(B) TYPE: amino acid

(D) TOPOLOGY: linear

- A - R - Q - R - R - P -

INFORMATION FOR SEQUENCE ID NO 284

(A) LENGTH:

(B) TYPE: amino acid

(D) TOPOLOGY: linear

- R - D - D - N - D - R - D - P - S - A - K -

SCHISTOSOMIN

INFORMATION FOR SEQUENCE ID NO 285

(A) LENGTH·

(B) TYPE: amino acid

(D) TOPOLOGY: linear

- K - V - S - K - R - P - D - Y - D -

INFORMATION FOR SEQUENCE ID NO 286

(A) LENGTH:

(B) TYPE: amino acid

(D) TOPOLOGY linear

- E - A - F - E - C - F - E - S - D - P - N - A - K -

INFORMATION FOR SEQUENCE ID NO 287

(A) LENGTH:

(B) TYPE: amino acid

(D) TOPOLOGY: linear

- K - C - R - K - K - Y - E - F - C - R -

APOLIPOPROTEIN(a)   HUMAN

INFORMATION FOR SEQUENCE ID NO 288

(A) LENGTH·

(B) TYPE: amino acid

(D) TOPOLOGY linear

-H-R-H-Q-R-T-P-E-N-Y-P-N-D-

INFORMATION FOR SEQUENCE ID NO 289
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-P-S-I-R-W-E-Y-C-

APOLIPOPROTEIN(a)   RHESUS
INFORMATION FOR SEQUENCE ID NO 290
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-Q-H-K-R-T-P-E-N-H-P-N-D-D-

INFORMATION FOR SEQUENCE ID NO 291
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-M-D-P-S-V-R-R-E-Y-C-

INFORMATION FOR SEQUENCE ID NO 292
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-T-P-E-N-Y-P-N-G-

INFORMATION FOR SEQUENCE ID NO 293
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-L-E-A-P-S-K-Q-A-

INFORMATION FOR SEQUENCE ID NO 294
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear

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-L-E-A-F-L-Q-E-P-T-E-E-

INFORMATION FOR SEQUENCE ID NO 295
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-G-H-L-A-G-G-T-D-R-

HEPATITIS DELTA ANTIGEN
INFORMATION FOR SEQUENCE ID NO 296
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-R-R-K-D-R-G-G-R-E-D-

INFORMATION FOR SEQUENCE ID NO 297
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-S-R-K-N-R-G-G-R-E-E-

INFORMATION FOR SEQUENCE ID NO 298
(A) LENGTH.
(B) TYPE. amino acid
(D) TOPOLOGY. linear
-E-S-K-G-K-R-A-G-R-E-Q-

REV PROTEIN HIV, SIV, VILV, OMVVS
INFORMATION FOR SEQUENCE ID NO 299
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY linear
-K-E-G-F-R-N-K-V-P-C-L-Q-E-

INFORMATION FOR SEQUENCE ID NO 300
(A) LENGTH.
(B) TYPE amino acid
(D) TOPOLOGY linear

-G-E-E-E-L-R-R-R-L-R-

INFORMATION FOR SEQUENCE ID NO 301
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-H-E-R-E-E-E-L-R-K-R-L-R-

INFORMATION FOR SEQUENCE ID NO 302
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-T-E-E-E-L-R-R-R-L-R-

INFORMATION FOR SEQUENCE ID NO 303
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-N-E-E-E-L-R-R-R-L-R-

INFORMATION FOR SEQUENCE ID NO 304
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-R-A-D-E-E-G-L-Q-G-K-L-R-

INFORMATION FOR SEQUENCE ID NO 305
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-D-S-D-E-E-L-L-R-T-V-R-

INFORMATION FOR SEQUENCE ID NO 306
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-E-P-Q-D-D-A-R-L-L-Q-A-V-K-

INFORMATION FOR SEQUENCE ID NO 307
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- P - E - E - R - R - L - L- B-

INFORMATION FOR SEQUENCE ID NO 308
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- W - R - D - M - E - P - P - L - R - E -

INFORMATION FOR SEQUENCE ID NO 309
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- W - R - D - M - E - P - P - L - R - E-

INFORMATION FOR SEQUENCE ID NO 310
(A) LENGTH.
(B) TYPE. amino acid
(D) TOPOLOGY linear
- Q - K - S - M - E - P - P - L - R - E -

INFORMATION FOR SEQUENCE ID NO 311
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - K - K - R - G - W - Y - K - W - L - R - K - L-

INFORMATION FOR SEQUENCE ID NO 312
(A) LENGTH:
(B) TYPE. amino acid
(D) TOPOLOGY linear
- K - R - R - K - G - W - F - Q - W - L - R - K - L-

ANGIOTENSINOGEN
INFORMATION FOR SEQUENCE ID NO 313
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - R - V - Y - I - H - P - F - H - L- L- Y - H - N - K-

INFORMATION FOR SEQUENCE ID NO 314
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - R - V - Y - I - H - P - F - H - L- L - Y - Y - S - K-

INFORMATION FOR SEQUENCE ID NO 315
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- D - R - V- Y - I - H - P - F - H - L- V - I - H - N - E-

INFORMATION FOR SEQUENCE ID NO 316
(A) LENGTH
(B) TYPE· amino acid
(D) TOPOLOGY linear
- E - N - P - S - V - E - T - L- P - E - S - T - F-

INFORMATION FOR SEQUENCE ID NO 317
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- E - N - P - S - V- E - T - L- P - E - P - T- F-

INFORMATION FOR SEQUENCE ID NO 318
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY linear
- A - K - A - N - A - G - K - P - K - D - P - T- F-

INFORMATION FOR SEQUENCE ID NO 319
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K- L- S - N - D - R - I - R - V- G- E-

INFORMATION FOR SEQUENCE ID NO 320
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K- M - G - D - T- N - P - R - V - G - E-

INFORMATION FOR SEQUENCE ID NO 321
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- N - I - G - D - T- N - P - R - V- G- E-

INFORMATION FOR SEQUENCE ID NO 322
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- E- L- E- A - D - E - R - E - P - T- E-

PRORENIN
INFORMATION FOR SEQUENCE ID NO 323
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- D - G - W - R - R - M - P-

INFORMATION FOR SEQUENCE ID NO 324
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- D - R - R - R - M - P-

INFORMATION FOR SEQUENCE ID NO 325
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-K-R-I-F-L-K-R-M-P-S-I-R-E-

INFORMATION FOR SEQUENCE ID NO 326
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-G-R-I-L-L-K-K-M-P-S-V-R-E-

INFORMATION FOR SEQUENCE ID NO 327
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-K-R-M-P-S-I-R-E-S-L-K-E-R-G-

INFORMATION FOR SEQUENCE ID NO 328
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-K-K-M-P-S-V-R-E-I-L-E-E-R-G-

INFORMATION FOR SEQUENCE ID NO 329
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-E-I-L-E-E-R-G –

INFORMATION FOR SEQUENCE ID NO 330
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY: linear
-R-L-G-P-E-W-S-Q-P-M-K-R-

INFORMATION FOR SEQUENCE ID NO 331
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-I-S-A-E-W-G-E-F-I-K-K-

INFORMATION FOR SEQUENCE ID NO 332
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-I-S-A-E-W-G-E-F-I-K-K-

INFORMATION FOR SEQUENCE ID NO 333
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
-R-L-S-A-E-W-G-V-F-T-K-R-

INFORMATION FOR SEQUENCE ID NO 334
(A) LENGTH·
(B) TYPE· amino acid
(D) TOPOLOGY: linear
-H-K-L-F-D-A-S-D-S-S-S-Y-K-H-

INFORMATION FOR SEQUENCE ID NO 335
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
-H-N-L-Y-D-S-S-E-S-S-S-Y-M-E-

INFORMATION FOR SEQUENCE ID NO 336
(A) LENGTH
(B) TYPE· amino acid
(D) TOPOLOGY linear
-H-S-L-Y-E-S-S-D-S-S-S-Y-M-E-

INFORMATION FOR SEQUENCE ID NO 337
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - E - D - V - F - S - F - S - F - Y - Y - N - R - D - S - E - N -

INFORMATION FOR SEQUENCE ID NO 338
(A) LENGTH:
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- K - E - E - V - F - S - V - Y - Y - N - R - G - S - H -

INFORMATION FOR SEQUENCE ID NO 339
(A) LENGTH:
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- D - P - Q - H - Y - E - G - N - F - H -

INFORMATION FOR SEQUENCE ID NO 340
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - K - L - M - E - A - L - G - A - K - K - R - L - F - D -

INFORMATION FOR SEQUENCE ID NO 341
(A) LENGTH·
(B) TYPE· amino acid
(D) TOPOLOGY: linear
- Q - L - I - M - Q - A - L - G - V - K - E - K - R - A - N -

INFORMATION FOR SEQUENCE ID NO 342
(A) LENGTH:
(B) TYPE amino acid
(D) TOPOLOGY. linear
- K - L - I - M - Q - A - L - G - A - K - E - K - R - I - E -

INFORMATION FOR SEQUENCE ID NO 343
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - V - F - Q - E - S - Y - S - S - K - K -

INFORMATION FOR SEQUENCE ID NO 344
(A) LENGTH·
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - Y - V - Q - K - N - P - F - R - N - D - D -

INFORMATION FOR SEQUENCE ID NO 345
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- D - Y - V - Q - Y - P - N - R - R - D - K -

INFORMATION FOR SEQUENCE ID NO 346
(A) LENGTH
(B) TYPE· amino acid
(D) TOPOLOGY· linear
- R - K - F - Y - T - E - F - D - R - R - N - N - R -

INFORMATION FOR SEQUENCE ID NO 347
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- R - K - F - Y - T - E - F - D - R - H - N - N - R -

INFORMATION FOR SEQUENCE ID NO 348
(A) LENGTH
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- R - K - F - Y - T - E - F - D - R - H - N - N - R -

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CORTICOTROPIN RELEASING FACTOR BINDING PROTEIN
INFORMATION FOR SEQUENCE ID NO 349
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - Y - L - E - L - R - E - A - A - D - Y - D -

INFORMATION FOR SEQUENCE ID NO 350
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - Y - L - E - V - Q - E - A - A - V - Y - D -

INFORMATION FOR SEQUENCE ID NO 351
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- K - R - D - V - A - G - E - Q - P - Y - R - R -

INFORMATION FOR SEQUENCE ID NO 352
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY· linear
- K - R - N - L - A - E - E - Q - P - Y - R - R -

INFORMATION FOR SEQUENCE ID NO 353
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - H - P - L - P - S - A - E - R -

INFORMATION FOR SEQUENCE ID NO 354
(A) LENGTH.
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - H - P - L - P - T - R - E - R -

INFORMATION FOR SEQUENCE ID NO 355
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - R - S - I - R - S - S - Q -

INFORMATION FOR SEQUENCE ID NO 356
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- R - R - S - V - T - S - S - Q -

INFORMATION FOR SEQUENCE ID NO 367
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - P - S - K - M - T - P - L - A - D -

INFORMATION FOR SEQUENCE ID NO 358
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- D - T - S - K - M - M - L - L - V - D -

INFORMATION FOR SEQUENCE ID NO 359
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - P - Y - E - L - E - N - P - N - G -

INFORMATION FOR SEQUENCE ID NO 360
(A) LENGTH:
(B) TYPE: amino acid
(D) TOPOLOGY: linear
- E - P - L - E - L - E - T - S - T - R -

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CLAIMS

What is claimed is:

1. A method to identify signal oligopeptides determining the action and interaction of a selected protein by determining the peptide regions of maximum hydrophylicity within the amino acid sequence (primary structure) of this protein. The regions of maximum hydrophylicity are identical with the signal oligopeptides of a protein.

2. A method to determine potential signal oligopeptides within a selected protein by use of a protein sequence database in combination with algorithms for hydrophylicity, and/or surface probability and/or other algorithms or their modifications as listed in Table 1 of this patent.

3 A method to identify, and develop xenologous signal oligopeptides as vaccines in the prevention and treatment of human diseases by making specific use of the technology described in detail in this patent. Effective vaccines to intercept the action of pathogenicity-mediating or undesired actions of selected human proteins can be produced by selecting the human protein, identifying the hydrophylicity peaks of this protein, aligning this protein to the same proteins *from other species*, selecting the corresponding xenologous hydrophylicity peaks, developing immunogenic therapeutic peptides on the basis of these xenologous signal oligopeptides (For details see figures 1,3,5-7 and Table 2-3).

4. A method to titrate the therapeutic efficacy of xenologous signal oligopeptides by making use of the evolutionary clock: The greater the genetic and evolutionary distance of the selected animal species, the greater the variation of amino acid residues particularly within the signal sequence of these proteins, the greater the antigenicity of these signal sequences, and the greater the therapeutic clinical efficacy of synthetic oligopeptide vaccines identical with these xenologous signal oligopeptide sequences of a selected protein

5 The use of the specific oligopeptide sequences No 1 to No 360 of this patent, as well as of the specific ①
sequences of earlier patent applications with the serial numbers 07/997,734; 07/997,727; 08/045,394
for the design, development, and use of therapeutic and diagnostic agents in the following specific way:

a) As therapeutic agents to function as direct competitive inhibitor(s) to specifically prevent or reduce the metabolic action or interaction of a selected protein by partially or completely blocking its specific signal sequences (For details see figure 1,2 and 6)

b) As therapeutic agents to function as feed-back regulators to specifically prevent or reduce the synthesis rate a selected protein (For details see figure 1 and 4)

c) As therapeutic agents in form of vaccines preferentially applied subcutaneously or intracutaneously with the aim to stimulate a specific immune response which can partially or completely block or decrease specific metabolic communication(s) Therapeutic peptides analogous to human protein sequences used

① including the modification of these sequences
according to claim # 6 of the present application

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as vaccines could be coupled to haptens to enhance immune response and thereby therapeutic efficacy (For details see figure 1, 3, 5-7 and table 2-3).

c) As vaccines for the production of specific and epitope-defined antibodies for *in vitro* use in a variety of diagnostic purposes (For details see figure 1 and 8).

6. Synthetic analogs to the specific oligopeptide sequences No 1 to No 360 of this patent, as well as of the specific sequences of earlier patent applications with the serial numbers 07/997,734; 07/997,727; 08/045,394 which vary from the sequences given in *one or more* of the following ways:

a) by omitting one or more of the amino residues at the *N -terminal end* (start of sequence given)

b) by omitting one or more amino acid residues at the *C-erminal end* (end of the sequence give)

c) by omitting one or more amino acid residues at the N-terminal *and* the C-terminal end of the sequence given

d) by substituting one or more of the amino acid residues within the given sequence without consideration of charge and polarity of the substitution residue

e) by substituting one or more of the amino acid residues within the given sequence with amino acid residues with similar charge and/or polarity

f) by omitting one or more amino acid residues within the given sequence

g) by a combination of two or more of the above modifications.